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REVIEW

Mechanism of action of the bile acid receptor TGR5 in obesity

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Abstract G protein-coupled receptors (GPCRs) are a large family of membrane protein receptors, and Takeda G protein-coupled receptor 5 (TGR5) is a member of this family. As a membrane receptor, TGR5 is widely distributed in different parts of the human body and plays a vital role in regulating metabolism, including the processes of energy consumption, weight loss and blood glucose homeostasis. Recent studies have shown that TGR5 plays an important role in glucose and lipid metabolism disorders such as fatty liver, obesity and diabetes. With the global obesity situation becoming more and more serious, a comprehensive explanation of the mechanism of TGR5 and filling the gaps in knowledge concerning clinical ligand drugs are urgently needed. In this review, we mainly explain the anti-obesity mechanism of TGR5 to promote the further study of this target, and show the electron microscope structure of TGR5 and review recent studies on TGR5 ligands to illustrate the specific binding between TGR5 receptor binding sites and ligands, which can effectively provide new ideas for ligand research and promote drug research.

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1. Introduction

Obesity is a complex and multifactorial disease. Study data show that between 1975 and 2016, the worldwide age-standardized obesity prevalence increased by 4.9% for girls and 6.9% for boys[1]. The global incidence of overweight and obesity has doubled since 1980, and nearly one-third of the world's population now falls into the category of overweight or obese[2]. Today, smoking ranks first among the causes of preventable diseases and deaths in the United States followed by obesity. According to the assessment, approximately 300,000 people die from obesity each year[3]. Internationally, a height and weight index (body mass index, BMI) is used to assess obesity status[4,5]. According to the WHO, the range of overweight in BMI is 25 to 30 (kg/m^2), while obesity is above 30.0 (kg/m^2)[6]. Obesity is often accompanied by dyslipidemia, hypertension, and impaired glucose tolerance and is also a risk factor for various illnesses, such as type 2 diabetes mellitus (T2DM), fatty liver, atherosclerosis, and gallstones[7,8]. Obesity has become a serious public problem in this era. Due to the gradual improvement in living conditions, the number of people with obesity is on the rise. Thus, the prevention and treatment of obesity urgently need to be addressed. Emerging studies in recent years have found that bile acids (BAs) play a vital role in maintaining metabolic homeostasis and have great potential to become a new target for preventing and treating obesity and related metabolic diseases.

BAs, one of the main components of bile, are synthesized in the liver and excreted into the duodenum through the secretion of bile under dietary stimulation. They can help with the absorption of nutrients and, regulate the growth of gut microbes. Moreover, they can regulate glucose homeostasis, triglycerides, cholesterol, and energy and can modulate self-synthesis and enterohepatic recirculation. Thus, while BAs are considered important molecules for the absorption of lipid substances and fat-soluble vitamins, they are also considered signalling factors with multiple endocrine and paracrine functions[7,9]. The premise for BAs playing the above role is that in tissues and organs with BA receptors, such as TGR5[10] and farnesol X receptor (FXR), the receptors combine with the associated BAs to send out signals and then regulate downstream genes, thus regulating metabolism in the body[11–13]. Among these receptors, TGR5 has attracted much attention in obesity, inflammation, and nonalcoholic fatty liver disease. However, reviews on the anti-obesity effect of TGR5 are relatively rare. An early literature report briefly introduced the biological principle of TGR5, and summarized the development of TGR5 regulators, but it lacked an explanation of the TGR5 mechanism[7]. Some literature studies have introduced the partial metabolic regulation of TGR5 in the treatment of liver disease[11,14]. While some articles aim at expounding the regulation of bile acid metabolism by TGR5, they also mention this bile acid receptor's ability to the regulate energy homeostasis, blood glucose and immunity[15,16]. Nevertheless, there are still some problems, for example, the mechanism of action has not been fully explained. This review will comprehensively discuss the regulatory effect of TGR5 on obesity-related mechanisms.

2. The bile acid receptor TGR5

GPCRs are a general term for a large type of membrane protein receptor, and their stereo structure contains seven transmembrane domains that play a crucial role in a variety of pathways[17]. As a member of the GPCR family, TGR5 is a GPCR that is coupled with stimulating adenylate cyclase G protein. TGR5 is also referred to as GPBAR1, M-BAR, and BG37 and was first discovered by Japanese scholar Takaharu Maruyama in 2002[18]. As a membrane receptor, TGR5 is widely distributed in tissues and organs of humans and rodents, including the liver, gallbladder, intestine, kidney, spleen, brain, skeletal muscle, brown adipose tissue (BAT), etc.[19,20]. Most of the effects on systemic metabolism attributed to BAs are regulated by TGR5, including the prevention of obesity, insulin resistance, liver steatosis and atherosclerosis caused by a high-fat diet[21]. Activation of TGR5 expressed by intestinal endocrine L cells can promote the secretion of glucagon-like peptide 1 (GLP-1), inhibit liver fat production, maintain glucose homeostasis, contribute to the improvement in islet function, and play a significant role in T2DM[22]. Moreover, the activation of the TGR5-type 2 deiodinase (D2) pathway effectively promoted the expression of thermogenic genes and stimulated the energy consumption of BAT and muscle and the oxidative phosphorylation of mitochondria[22,23]. TGR5 agonists can effectively improve liver steatosis and insulin sensitivity in mice fed a Western diet and have therapeutic potential for nonalcoholic fatty liver disease or nonalcoholic steatohepatitis[24].

In addition, widely expressed TGR5 also plays a role in inflammation, intestinal injury, primary sclerosing cholangitis and so on. Yuan et al.[25] reported that TGR5 upregulated the expression of cyclic adenosine monophosphate (cAMP) in rat alveolar macrophages, decreased the activity of macrophages, and effectively inhibited the production of proinflammatory factors induced by lipopolysaccharide. TGR5 inhibits the expression of Toll-like receptor 4 induced by lipopolysaccharide, thus reducing the expression of inflammatory cytokines[26,27]. In the gut, BAs promote intestinal healing by activating TGR5 in intestinal stem cells under the dual mechanism of the anti-inflammatory action of intestinal immunocytes and by promoting the renewal of epithelial cells[28,29]. TGR5 expressed in bile duct epithelial cells can trigger cell proliferation and prevent apoptosis; effectively reduce inflammation of the whole body, liver and intestinal tract; and play a potential protective role in primary sclerosing cholangitis[30].

Currently, as signalling molecules, BAs play a crucial role in the prevention/treatment of metabolic diseases, and the widely expressed TGR5 has also become an important molecule. The Protein Data Bank (PDB) first showed the cryogenic electron microscope structure of the complex of TGR5 and synthetic agonist 23H (PDB Code: 7BW0). TGR5 presents a ligand-binding cavity in the extracellular region. The agonist 23H interacts with the residues of transmembrane helical proteins TM2, TM3, TM5 and TM6 on the orthosteric site of TGR5, but mutation of the residue significantly affects the potency of 23H[31]. Another TGR5 agonist, R399, is complexed in the cavity with a "V" shape. Similarly, the change in structural site residues will affect the

induction of cAMP accumulation by R399. The difference is that after complexing with R399, TGR5 tends to activate β-arrestin1 signalling and to stimulate cell proliferation. On the other hand, when complexing with INT-777, which is also an agonist, priority is given to activating GPBAR-Gs signalling, inhibiting cell proliferation and inducing apoptosis. The reason for this difference is that different ligands have different complexed residual sites with TGR5, which leads to biased activation of the signal[32]. Unexpectedly, the study found that there is a second ligand-binding cavity in TGR5. Ligands containing only 12-hydroxyl groups (such as CA, DCA, GCA, TCA, TDCA, and INT-777) complexed with their cavity residues allosterically regulated receptor activity and showed the effect of positively activating TGR5 in cooperation with the first cavity agonist[33] (Fig. 1). This result shows an important aspect that needs to be considered in future research involving TGR5 agonist discovery or artificial design and synthesis. That is, through the understanding of the complete function of the residues on the TGR5 receptor and combining the corresponding residue sites according to the required functions, agonists can be designed reasonably and accurately designed.

3. Synthesis and metabolism of BAs

3.1. *Synthesis of BAs*

As the natural ligand of TGR5, fully understanding the BA synthetic pathway will help us to better understand the role of TGR5 in regulating metabolism. According to the structure type, BAs can be classified into free and bound BAs; additionally, they can be classified into primary and secondary types according to the source classification. BAs are amphiphilic steroid molecules synthesized by the utilization of perihepatocyte cholesterol and 15 related enzymes[15]. The process mainly includes pathways such as the classic pathway and the alternative pathway.

In the first step of the classic pathway, cholesterol is converted to 7α-cholesterol under the action of CyP7A1 and then to C4 under the action of HSD3B7. As the transformation precursor of cholic acid (CA) and chenodeoxycholic acid (CDCA), the serum level of C4 reflects the rate of BA synthesis in the human body. C4 is hydroxylated to 7,12-dihydroxycholest-4-*en*-3-one under the catalysis of CYP8B1 and is then converted to 3,7,12-trihydroxycoprostane by two aldehyde and ketone reductases (AKR1D1 and AKR1C4). In the absence of CYP8B1 hydroxylation, C4 is converted to dihydroxycoprostane. In the presence of CYP27A1, 3,7,12-trihydroxycoprostane and dihydroxycoprostane form THCA and DHCA, respectively. Subsequently, the steroid side chain cleavage reaction of THCA and DHCA occurs under the action of peroxisomes and forms bile coenzyme A and chenodeoxycholic acid coenzyme A. This process is similar to the β oxidation of fatty acids. The peroxisomal protein BAAT enables cholyl coenzyme A and chenodeoxycholyl coenzyme A to combine with taurine (T) or glycine (G), respectively, to form taurine/glycine CA (T/G-CA) and taurine/glycine CDCA (T/G-CDCA). When the bound BAs T/G-CA and T/G-CDCA are secreted into the intestine, bacterial bile salt hydrolase (BSH) in the intestinal tract dissociates taurine and glycine to form the free BAs CA and CDCA, followed by the formation of deoxycholic acid (DCA) and lithocholic acid (LCA) under the action of bacterial 7α-dehydroxylase[9,14,34–36].

The alternative pathway of BA synthesis begins with the catalytic reaction of the hydroxylase CYP27A1 in the liver, macrophages and suprarenal gland. Under the two-step catalysis of CYP27A1, cholesterol is converted to 27-hydroxycholesterol and then to cholestenoic acid. With the action of CYP7B1, cholestenoic acid is converted to 3,7-dihydroxy-5-cholestenoate, and then 7α-hydroxy-3-oxo-4-cholestenoate is formed by the action of HSD3B1/3B2. Additionally, the cyclases CYP46A1 and CH25H, which exist in the brain and liver, respectively, are also involved in the alternative pathway of BA synthesis. In the brain, cholesterol is converted to 24-hydroxycholesterol by CYP46A1, and 24-hydroxycholesterol is then hydroxylated to 7,24-dihydroxycholesterol by the liver hydroxylase CYP39A1. In the livers of mice and humans, cholesterol is hydroxylated by CH25H to form 25-hydroxycholesterol, which is converted to 7α,25-dihydroxycho lesterol under the action of CYP7B1. These oxidized sterols are transported to the liver as precursors of BAs and undergo further conversion[37,38].

In humans, the bacterial dehydrogenase 7β-HSDH can convert a small amount of CDCA in the intestinal tract into ursodeoxycholic acid. In mice, most CDCA is further transformed to α-murocholic acid (α-MCA) by the hydroxylase Cyp2c70 and is then transformed into its 7β-differential isomer, β-murocholic acid (β-MCA), by 7α-β-differential isomerase. Furthermore, Cyp2c70 is able to hydroxylate UDCA to β-MCA. Mouse BAs are almost exclusively bound to taurine, with a small amount bound to glycine. In addition, α/β-MCA combined with taurine can form ω-murocholic acid (ω-MCA) through deconjugation and dehydroxylation[39,40] (Fig. 2).

3.2. *Enterohepatic circulation of bile acid*

In the human body, the conversion of cholesterol is involved in the homeostasis of cholesterol and prevents the accumulation of cholesterol and triglycerides as well as damage to the liver and other organs. The resulting BAs play a key role in promoting the absorption and distribution of nutrients, regulating metabolism and maintaining balance in the body's enterohepatic circulation[41].

After cholesterol is successfully converted to BAs, BAs are transported from the tubule membrane to the gallbladder for storage through the bile salt export pump (BSEP). Under the stimulus of feeding, BAs are secreted through the duodenal papilla and act as detergents and signalling molecules in the intestine. Most of the BAs in the intestinal cavity can be reabsorbed by the apical sodium-dependent bile acid transporter (ASBT) at the end of the ileum. The reabsorbed BAs can be delivered to the portal vein through the organic solute transporter α/β (OSTα/β) in the basolateral membrane of intestinal cells. Then, BAs return to the liver through the portal vein circulation and enter hepatocytes under the action of sinusoidal sodium-taurocholate cotransporting polypeptide (NTCP)[42,43] (Fig. 3).

Human BA pools contain 2−4 g of BA, and BA/salt circulation between the liver and intestines takes place 6−10 times a day, transporting 20 to 40 g of BA. However, 0.2−0.6 g of BA per day is consumed in the enterohepatic circulation pathway and excreted in the faeces, and this amount of BA must be replenished by cholesterol from scratch[44]. LCA is a special case. Its content is very low, and it is hepatotoxic at high concentrations. In the enterohepatic circulation, LCA is sulfated and excreted in the faeces before it is secreted into bile[44].

4. Natural and synthetic ligands of TGR5

In the original TGR5 study, Kawamata et al.[45] screened more than 1000 compounds by measuring luciferase activity and

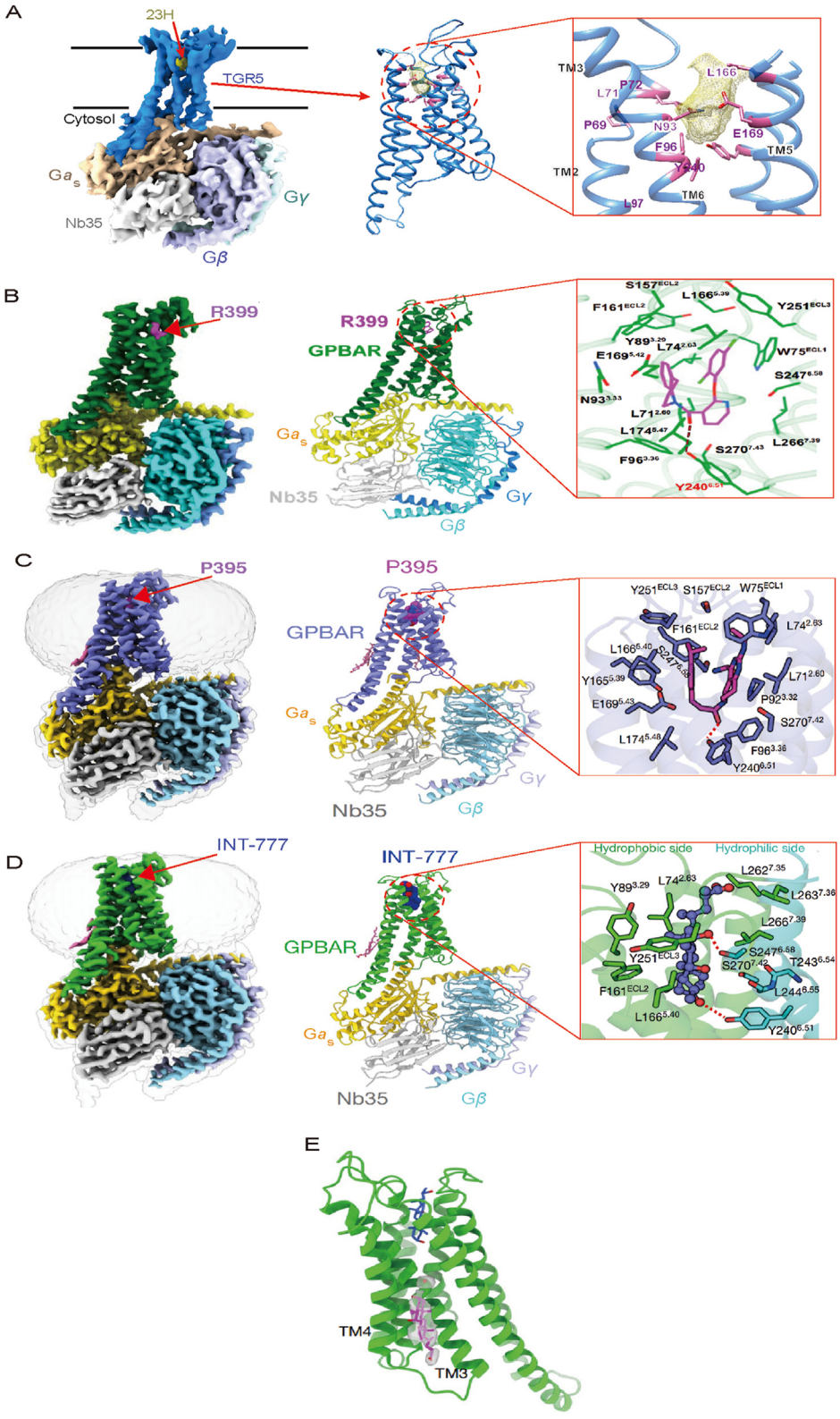


Figure 1 Cryogenic electron microscope structure of TGR5 complexes. (A) 23-H/TGR5 complex. Reproduced with permission from Ref. 31. Copyright © 2020, Springer Nature. (B) R399/TGR5 complex. Reproduced with permission from Ref. 32. Copyright © 2022, Proceedings of the National Academy of Sciences. (C) P395/TGR5 complex. (D) INT-777/TGR5 complex. (E) INT-777 simultaneously complexes two ligand-binding cavities at the orthosteric and allosteric sites. Reproduced with permission from Ref. 33. Copyright © 2020, Springer Nature.

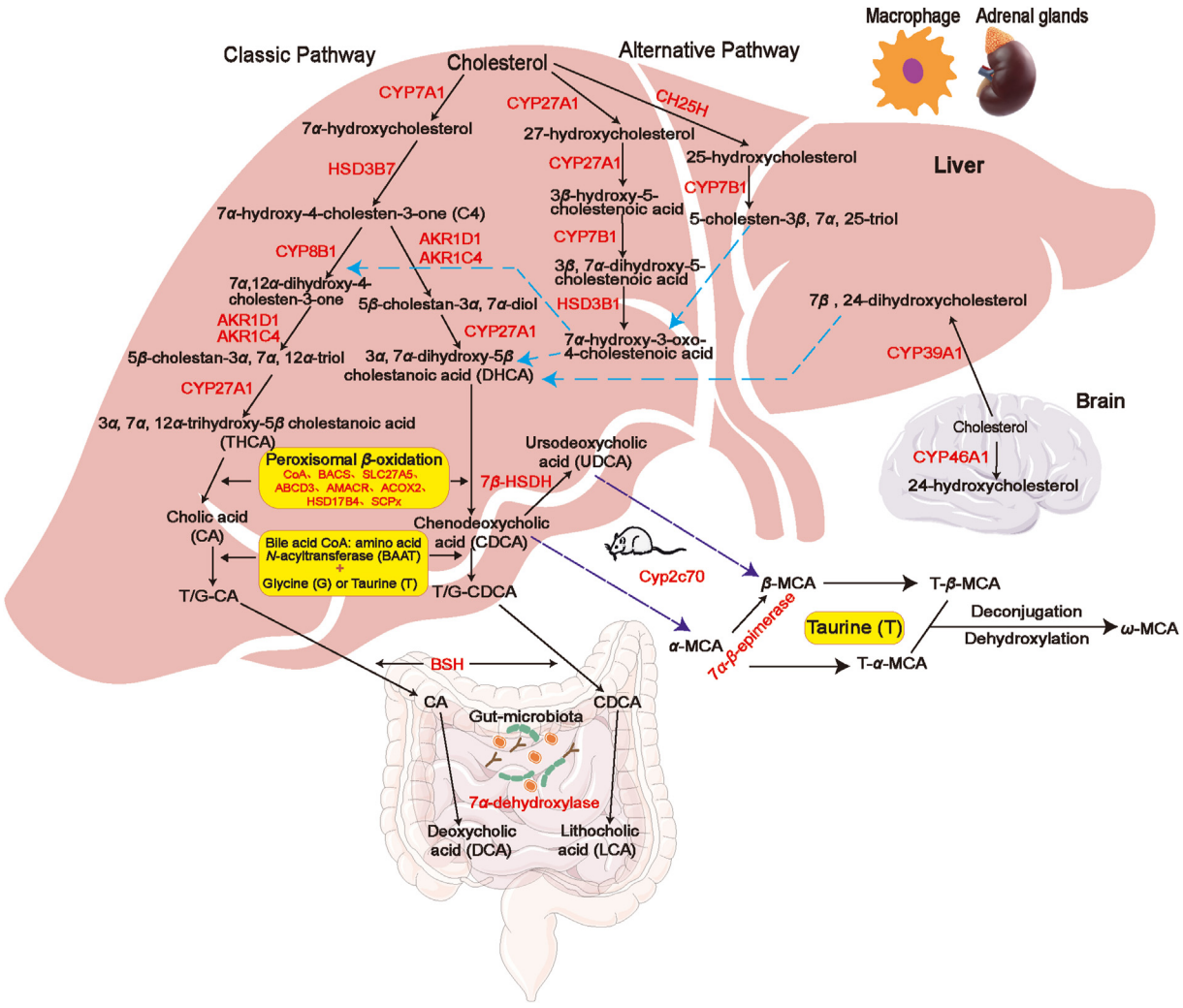


Figure 2 Bile acid synthesis pathways. In the classical pathway, cholesterol is converted to primary bile acids. The alternative pathway is the replacement of CYP7A1 by oxysterol 27α hydroxylase, dehydrogenation of cholesterol to oxysterol, followed by 7α dehydrogenation catalyzed by oxysterol 7α hydroxylase, and then into the classical pathway. Chole acid and chenodeoxycholic acid combine with glycine or taurine to form conjugated bile acids, which are excreted into the intestinal tract through the bile duct. Abbreviation: the rate-limiting enzyme cholesterol 7α hydroxylase (CYP7A1); 7α-hydroxy-4-cholestene-3-one (C4); 3β-hydroxyΔ5-C27-steroid dehydrogenase (HSD3B7); sterol 12-hydroxylase (CYP8B1); AKR1D1 and AKR1C4; sterol 27 hydroxylase (CYP27A1); 3α,7α,12α-trihydroxy-5β-cholestanoic acid (THCA); 3α,7α-dihydroxy-5β-cholestanoic acid (DHCA); bile acid CoA: amino acid *N*-acyltransferase (BAAT); steroid 24-hydroxylase (CYP46A1); sterol 25-hydroxylase (CH25H); oxysterol 7α-hydroxylase (CYP7B1); hydroxy-delta-5-steroid dehydrogenase, 3β- and steroid delta-isomerase 1/2 (HSD3B1/3B2); sterol 7-hydroxylase (CYP39A1); 7β-hydroxysteroid dehydrogenase (7β-HSDH); sterol-6β-hydroxylase (Cyp2c70).

detected that BAs [including taurolithocholic acid (TLCA), LCA, DCA, and CDCA] led to increased cAMP in *TGR5* gene-transfected cells. With the discovery of TGR5, identifying the BAs that activate TGR5 has once again become a research hotspot and has further aroused scientists' interest in the role of BAs as a hormone. With the in-depth study of TGR5, researchers are paying increasing attention to the important role of TGR5 in various physiological functions. Some studies have shown that TGR5 activation may have therapeutic efficacy and is likely to become a potential therapeutic target for several metabolic diseases. Therefore, the study of TGR5 agonists has also become a research direction.

Agonists of TGR5 can generally be divided into two main categories: natural compounds and synthetic agonists. These include BAs, semisynthetic BAs, and triterpenoids derived from plants[46].

4.1. *Endogenous BAs*

BAs were one of the earliest discovered agonists. Their agonistic effect on TGR5 varies with the type of BA, and the order is LCA>DCA>CDCA>CA>UDCA[47,48]. Compared with the nuclear receptor FXR, the most effective BA agonists of the membrane receptor TGR5 are hydrophobic BAs, and the combination with taurine further improves the potency of BA[44]. Using LCA as an agonist, Hsu et al.[49] observed that activation of cardiac TGR5 contributed to enhanced cardiac contractility and decreased heart rate in obese rats on a high-fat diet. Chen et al.[50] utilized a diet-induced obese mouse model to characterize the effect of the natural TGR5 ligand CDCA, and the experiments showed that CDCA can activate TGR5 to prevent high-fat diet-induced obesity and hyperglycaemia. In addition, Chaudhari et al.[51] found that gastrointestinal cholic acid 7-sulfate (CA7S) increased after

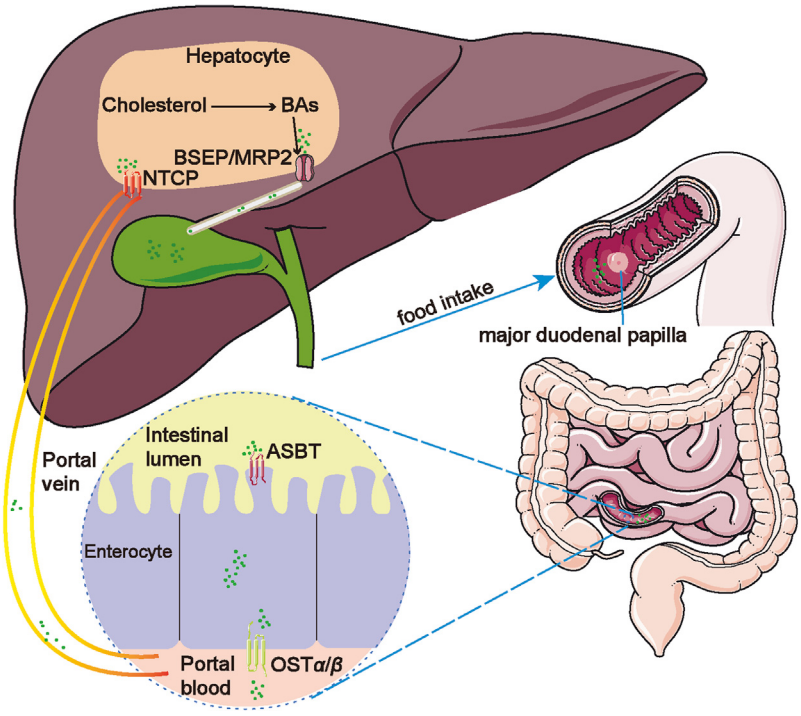


Figure 3 Enterohepatic circulation of bile acids. Primary bile acids are synthesized by cholesterol in the liver and are transported to and stored in the gallbladder. After stimulation of feeding, bile acid is excreted into the duodenum, emulsifying dietary lipids to aid absorption. Most of these bile acids circulate in the liver through reabsorption.

bariatric surgery, which played a role in glucose regulation, and the effect was limited to the intestinal tract.

However, BAs have the disadvantages of low affinity and specificity that is not limited to TGR5[52], so additional agonists that can meet these requirements are needed.

4.2. *Natural compounds*

In recent years, the use of plants in daily life as complementary and alternative medicine has increased, and they can also be used as a source of drug candidates for research in the pharmaceutical industry. Notably, approximately 45% of the drugs on the market come from plants[53]. Studies have shown that triterpenoids can effectively activate TGR5[54], and high-potency and safe TGR5 triterpenoid agonists are likely to become drugs for the treatment of diseases.

Sato et al.[55] identified the active triterpenoid oleanolic acid from olive leaves. The study confirmed that oleanolic acid helps to slow high-fat-induced weight gain and has strong anti-hyperglycaemic activity. Interestingly, oleanolic acid could not activate FXR but was a selective TGR5 agonist. Ladurner et al.[56] studied the activation of TGR5 by 19 kinds of plant extracts and screened three kinds of common flavour extracts, namely, SaroE (clove), PdioE (allspice), and KgalE (aromatic ginger), that can markedly improve the expression of TGR5. Further study found that the main component of SaroE and PdioE is triterpene acid (TTA), and the main constituents of TTA in SaroE are oleanolic acid and maslinic acid. PdioE contains less TTA, but there are four active components, namely, oleanolic acid, crategolic acid, corsolic acid and ursolic acid. However, KgalE was not successfully analysed for its active components in this study. Lo et al.[57] demonstrated the activation of TGR5 by betulinic acid through cell experiments for the first time, and the experiment also showed that betulinic acid could increase glucose uptake and induce the secretion of glucagon-like peptide in a dose-dependent manner. Regrettably, natural compounds that exist in nature still have various defects that have hindered their clinical use as drugs.

4.3. *Synthetic compounds*

To find TGR5 agonists suitable for disease treatment, scientists set out to screen various compounds from natural and synthetic compound libraries and to modify them to improve their potency and pharmacokinetics. Based on the consideration of the chemical structure and physicochemical properties of CA, Pellicciari et al.[58] synthesized a new TGR5 agonist, INT-777, with high efficiency and selectivity. Through the use of INT-777 and related experiments, Velazquez-Villegas et al.[21] proved that TGR5 activation can significantly reduce body weight and effectively promote beige remodelling of subcutaneous white adipose tissue. Sorrentino et al.[28] co-incubated wild-type mouse and TGR5$^{-/-}$ mouse intestinal organoids with the TGR5 agonist INT-777 to monitor intestinal stem cell function by morphological analysis and colony formation assays. The experimental results showed that INT-777 can promote the regeneration of intestinal epithelial cells. Genet et al.[54] selected betulinic acid with high TGR5 potency from a natural triterpene library as the lead compound in the study of structure−function relationships. It was found that diastereomer 18dia 2 of the 18th betulinic acid synthetic derivative has an excellent exciting effect *in vitro*. Unfortunately, although 18dia 2 is an effective TGR5 agonist, 18dia 2 shows low bioavailability *in vivo*. However, the triterpenoid skeleton of 18dia 2 is likely to contribute to the synthesis of better therapeutic drugs for TGR5 *in vivo*. Qian et al.[59] designed 14 new CA derivatives and found

that a new CA derivative, B1, can efficiently activate TGR5 and be used as a lead compound for further research. Suling Huang et al.[60] used MN6 (compound **22g**[61]), synthesized in previous studies, to show that activation of TGR5 can regulate blood glucose homeostasis and insulin resistance. Yu et al.[62] designed 23(*S*)-m-LCA with selective alkylation of C23(*S*) through stereoselective methodology, which effectively enhanced the ability of TGR5 to promote intestinal GLP-1 transcription. Cerra et al.[63] improved the synthesis of the TGR5/FXR double receptor agonist INT-767 and promoted the study of double receptor agonists. Dehmlow et al.[64] developed RO5527239 to improve the secretion of polypeptide YY (PYY) and GLP-1 in obese mice and stabilize blood sugar fluctuation. A novel TGR5 agonist compound **4d** cooperates with sitagliptin to promote GLP-1 secretion and regulate blood glucose, which provides a potential clinical choice for the treatment of T2DM[65]. Terui et al.[66] synthesized ligand compound **4b** with strong TGR5 agonist activity by using TMN (5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene) as the skeleton, which provides a potential drug choice for the treatment of dyslipidaemia. In addition, TGR5 agonists in the past 5 years are listed in Table 1[67–85].

Currently, the weight loss drugs examined and approved by the US Food and Drug Administration are roughly divided into two categories: pancreatic lipase inhibitors and appetite-suppressing anorexia drugs. The former can reduce the absorption of intestinal fat to achieve weight loss, while the latter can achieve weight loss by suppressing appetite and reducing the ingestion of food[86]. However, most of the weight loss drugs on the market have unpleasant side effects. Therefore, based on the function of TGR5 in regulating glucose and lipid metabolism, the development of effective and safe TGR5 agonist drugs can help us control obesity.

5. Mechanism of action of TGR5 in obesity

5.1. TGR5 promotes thermogenesis through the cAMP−PKA−D2 signalling pathway

When there is a large gap in the balance between energy intake and consumption, that is, when the intake far exceeds the energy consumption, the excess energy will be converted into fat for storage, and obesity occurs[87]. In the state of obesity, the number and size of adipocytes increase, a large amount of fat accumulates, and the function of adipose tissue shows a state of imbalance. Adipose tissue can be divided into three types: white adipose tissue (WAT), BAT and beige adipose tissue. WAT can store excess energy, BAT generates heat, and beige adipose tissue is transformed from WAT and stores energy. However, under certain conditions, beige adipose tissue can generate heat[86,88]. According to research, BAT plays an indispensable role in body weight, energy balance, and glucose metabolism[89], and the activation of BAT helps to increase energy consumption throughout the body[90], which also represents a promising strategy for the prevention of obesity in humans.

The thermogenic function of BAT depends on many mitochondria in brown adipocytes and the high expression of mitochondrial inner membrane uncoupling protein 1 (UCP1). In the process of mitochondrial synthesis of adenosine triphosphate, UCP1 can prevent the production of adenosine triphosphate (ATP) and release the energy obtained by oxidative decomposition of sugars, fats and amino acids in the form of heat[91]. In addition, the thermogenic function of BAT is also affected by thyroid hormone[92]. As the largest endocrine gland in the human body, the main active substances secreted by the thyroid gland are tetraiodothyronine (T4) and triiodothyronine (T3). Among them, T3 is considered, the active form of thyroid hormone because of its stronger affinity for the thyroid hormone receptor[93]. Research shows that T3 can stimulate the activation of BAT and promote heat production[94]. T3 effectively induced mitochondrial autophagy in BAT, increased the turnover rate such that synthesis exceeded the clearance of mitochondria, promoted mitochondrial biogenesis and maintained the integrity of BAT mitochondria during thermogenesis[95]. Moreover, T3 induced the expression of thermogenic genes (UCP1, PRDM16, and PGC-1α), fatty acid oxidation genes (CPT1B and ACSL1) and lipolysis genes (PNPLA2 and LIPE), which promoted metabolism in the body[95–98]. As the deiodination product of the pro-hormone T4, the serum level of T3 is much lower than that of T4, and increasing T3 levels may be an effective intervention for obesity. We have observed from a report that BAs promote the energy consumption of BAT by inducing intracellular thyroid hormone activation and effectively reduce body weight and improve insulin resistance in mice. TGR5 plays a key role in this process as a BA receptor[99]. TGR5, which is highly expressed in BAT promotes T3 transformation under the activation of BAs, and this pathway also involves the role of other related signalling molecules.

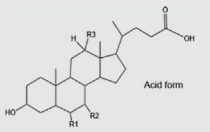
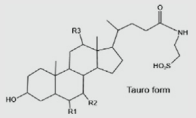
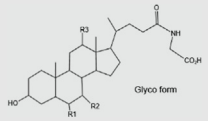
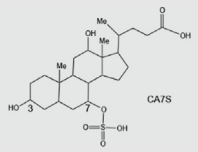
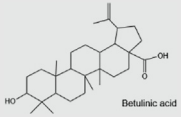
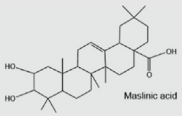
cAMP, as a secondary messenger, is regulated by positive feedback from TGR5. TGR5 agonists can rapidly and dose-dependently increase the level of cAMP[18]. In the activated state, the excitatory G protein subunit $G\alpha$ on TGR5 can induce the activation of adenyl cyclase (AC), and then AC catalyses the reaction with ATP to produce a large amount of cAMP[100]. With cAMP levels rising, cyclic-AMP dependent protein kinase A (PKA), which is finely regulated by cAMP, is also upregulated[101,102]. PKA plays a variety of functions in cells, including the regulation of cellular metabolism[103]. Interestingly, the activation of PKA can effectively upregulate the expression of D2[104], which connects the above pathways. D2 is a member of the deiodinase family and is very important for increasing the level of T3. D2 can effectively induce the deiodination of T4, thus greatly increasing T3 content and promoting energy consumption and fatty acid and fat metabolism[105–107].

In addition, this signalling pathway not only plays the above role in BAT, but also promotes thermogenesis and energy consumption in skeletal muscles that simultaneously express TGR5 and D2 in the same way[99,108]. The complete presentation of the TGR5−cAMP−PKA−D2−T3 signalling pathway demonstrates the effect of TGR5 on thermogenesis in BAT and provides a good target for studying the direction of BAT in the treatment of obesity (Fig. 4).

5.2. TGR5 promotes the browning of white adipose tissue

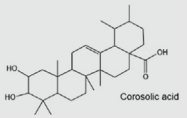
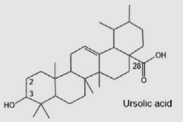
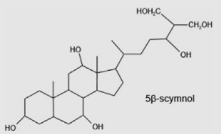
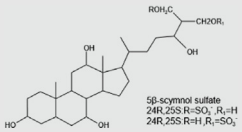
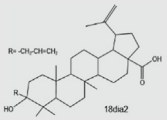
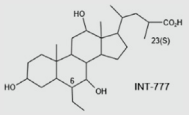
White adipocytes can undergo a process of “browning”; that is, brown adipocytes appear in WAT. These brown adipocytes are also known as beige adipocytes and produce heat[109,110]. Cold exposure is an effective inducer of “browning”[111], and TGR5 is indispensable in this transformation process. After one week of cold exposure (8 °C), “browning” occurred in the subcutaneous white adipose tissue (scWAT) of wild-type mice. In the state of browning, the expression of BAT-specific genes (UCP1, PGC-1α and PRDM16) and specific biomarkers of beige adipocytes is increased in WAT, and mitochondrial fission in white adipocytes is also promoted.

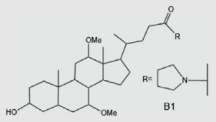
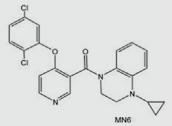
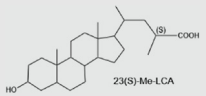
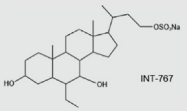
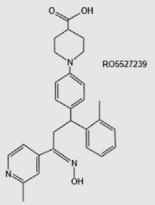
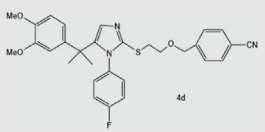
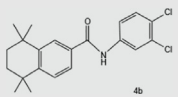
Table 1 Structure and potency of bile acids, natural compounds and synthetic compounds as TGR5 agonists.

Structure	Compd. name				EC_{50}			E_{max} (%)			Ref.
Bile acids											
	Name	R1	R2	R3	Acid form (μmol/L)	Tauro form (μmol/L)	Glyco form (μmol/L)	Acid form	Tauro form	Glyco form	45,48
	CA	H	α-OH	α-OH	13.6	4.95	13.6	101	104	103	
	CDCA	H	α-OH	H	6.71	1.92	3.88	105	103	105	
	DCA	H	H	α-OH	1.25	0.79	1.18	105	103	105	
	LCA	H	H	H	0.58	0.29	0.54	101	106	92	
	UDCA	H	β-OH	H	63.4	30.0	33.9	74.9	97	91	
											
											
	Cholic acid-7-sulfate				hTGR5: 0.17 μmol/L			No data			51
Natural compounds											
	Betulinic acid				mTGR5: 1.04 μmol/L			83			54
	Maslinic acid				hTGR5: 3.7 ± 0.7 μmol/L			29.2 ± 5.0			56

(*continued on next page*)

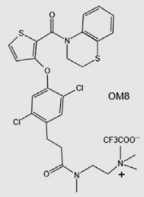
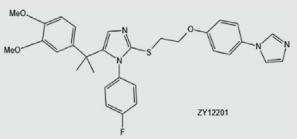
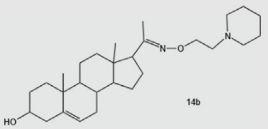
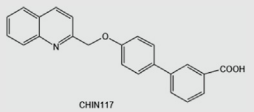
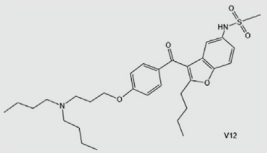
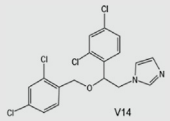
Table 1 (*continued*)

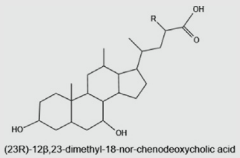
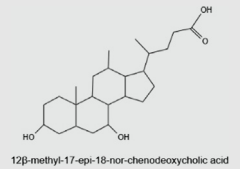
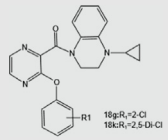
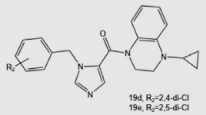
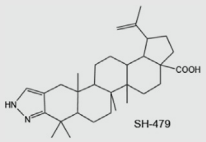
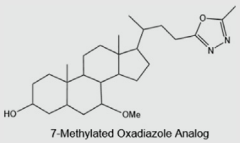
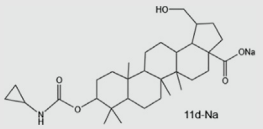
Structure	Compd. name	EC_{50}	E_{max} (%)	Ref.
	Corosolic acid	hTGR5: 0.5 ± 1.0 μmol/L	9.8 ± 3.3	56
	Ursolic acid	hTGR5: 1.1 ± 0.2 μmol/L	19.6 ± 14.2	56
	5β-Scymnol	No data	No data	67
	5β-Scymnol sulfate	No data	No data	
Synthetic compounds				
	Betulinic acid derivative (18dia 2)	mTGR5: 0.12 μmol/L	122	54
	CA derivative (INT-777)	mTGR5: 0.82 (0.54−1.24) μmol/L	166	58
	CA derivative (B1)	hTGR5: 0.15 ± 0.09 μmol/L	No data	59

				
	MN6 (**22g**)	hTGR5: 1.5 ± 0.21 μmol/L mTGR5: 18 ± 1.1 μmol/L	No data	61
	23(*S*)−Me-LCA	hTGR5: 0.22 μmol/L	No data	62
	INT-767	hTGR5: 0.68 ± 3 μmol/L	120 ± 5	63
	RO5527239	hTGR5: 4 nmol/L mTGR5: 2.8 nmol/L	102 163	64
	Compound **4d**	hTGR5: 2.3 μmol/L	No data	65
	Compound **4b**	hTGR5: 6.6 nmol/L	No data	66

(*continued on next page*)

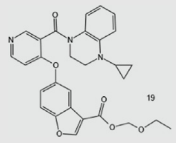
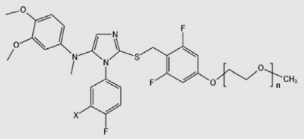
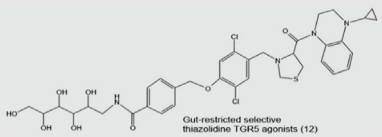
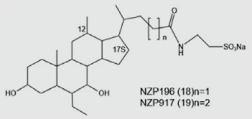
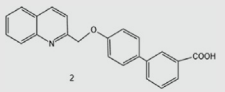
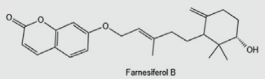
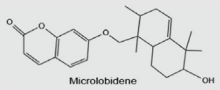
Table 1 (*continued*)

Structure	Compd. name	EC_{50}	E_{max} (%)	Ref.
	OM8	hTGR5: 202 ± 55 nmol/L mTGR5: 74 ± 17 nmol/L	No data	68
	ZY12201	hTGR5: 57 pmol/L mTGR5: 62 pmol/L	No data	69
	Pregnane-oximino-amino-alkyl-ether, **14b**	hTGR5: 3.058 nmol/L	No data	70
	CHIN117	hTGR5: 4.6 μmol/L	No data	71
	**V12**	hTGR5: 19.5 μmol/L	No data	72
	**V14**	hTGR5: 7.7 μmol/L	No data	72

 (23R)-12β,23-dimethyl-18-nor-chenodeoxycholic acid	(23*R*)-12β,23-Dimethyl-18-nor-chenodeoxycholic acid	hTGR5: 25 μmol/L	71	73
 12β-methyl-17-epi-18-nor-chenodeoxycholic acid	12β-Methyl-17-*epi*-18-nor-chenodeoxycholic acid	hTGR5: 25 μmol/L	59	73
 18g:R1=2-Cl 18k:R1=2,5-Di-Cl	3-Phenoxypyrazine-2-carboxamide derivatives (**18g**, **18k**)	hTGR5: **18g**: 1.44 nmol/L **18k**: 0.58 nmol/L mTGR5: **18g**: 119.6 nmol/L **18k**: 267.2 nmol/L	No data	74
 19d, R2=2,4-di-Cl 19e, R2=2,5-di-Cl	1-Benzyl-1H-imidazole-5-carboxamide derivatives (**19d**, **19e**)	hTGR5: **19d**: 6.8 ± 0.43 nmol/L **19e**: 9.5 ± 0.61 nmol/L mTGR5: **19d**: 611 ± 33 nmol/L **19e**: 832 ± 47 nmol/L	No data	75
 SH-479	SH-479	mTGR5: 0.81 μmol/L	No data	76,77
 7-Methylated Oxadiazole Analog	7-Methylated oxadiazole analog	mTGR5: 5.59 ± 0.66 nmol/L	No data	78
 11d-Na	11d-Na	hTGR5: 6.81 ± 1.8 nmol/L mTGR5: 914 ± 51 nmol/L	No data	79

(*continued on next page*)

Table 1 (*continued*)

Structure	Compd. name	EC_{50}	E_{max} (%)	Ref.
	Compound **19**	hTGR5: 16.4 ± 4.1 nmol/L mTGR5: 209 ± 31 nmol/L	No data	80
	PEGylated 5-amino-2-thio-imidazole	No data	No data	81
	Gut-restricted selective thiazolidine TGR5 agonists (**12**)	hTGR5: 143 nmol/L mTGR5: 1.2 nmol/L	No data	82
	NZP196 (**18**) and NZP917 (**19**)	hTGR5: 18: 0.31 μmol/L 19: 0.27 μmol/L	No data	83
	Compound **2**	hTGR5: 4.6 ± 1.5 μmol/L	No data	84
	Farnesiferol B	hTGR5: 13.53 μmol/L	No data	85
	Microlobidene	hTGR5: 13.88 μmol/L	No data	85

In the table above, EC_{50} refers to the half effective dose. E_{max} refers to % of 10 μmol/L LCA value. hTGR5: human TGR5, mTGR5: mouse TGR5.

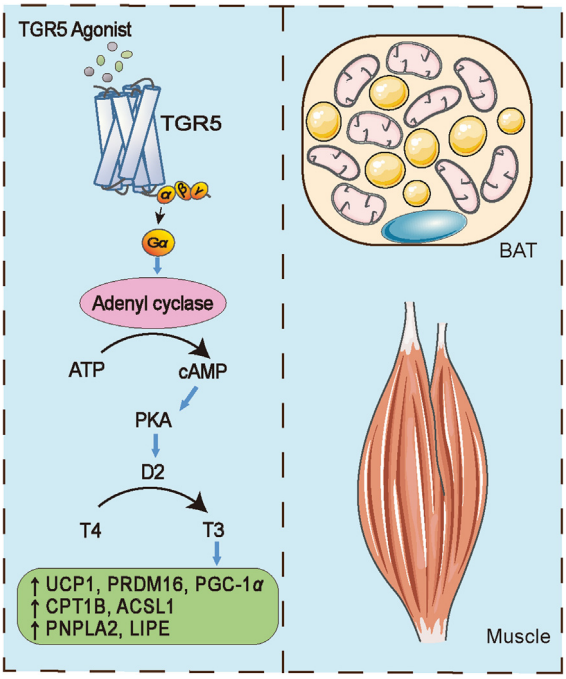


Figure 4 TGR5 promotes the expression of thermogenesis-related genes through cAMP−PKA−D2 signalling pathway and increases energy consumption. Abbreviation: PR domain-containing 16 (PRDM16); carnitine palmitoyltransferase 1B (CPT1B); acyl-CoA synthetase long chain family member 1 (ACSL1); patatin like phospholipase domain-containing protein 2 (PNPLA2); lipase E (LIPE).

Interestingly, administration of the TGR5 agonist INT-777 had the same effect. The activation of TGR5 promoted the phosphorylation of extracellular-regulated protein kinase (ERK) at serine 616, effectively activating dynamism-related protein 1 (DRP1), which is involved in mitochondrial division, and increased the expression of mitochondrial fission factor (MFF), which can recruit DRP1 to mitochondria. The two signalling pathways, that is, TGR5−MFF and TGR5−ERK−DRP1, play an important role in mediating mitochondrial fission and effectively increase the number of mitochondria and the thermogenic capacity of WAT[21]. Moreover, activated TGR5 can promote the phosphorylation of cAMP-response element binding protein (CREB) through the cAMP−PKA pathway[112,113]. CREB plays a critical role in modulating the transcription and expression of the mitochondrial thermogenic gene peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α)[114], and PGC-1α is the main regulator of UCP1. Moreover, TGR5 can increase mitochondrial mass and the mitochondrial/nuclear DNA ratio (mtDNA/nDNA) through the CREB-PGC-1α signalling pathway and can effectively improve mitochondrial function[115]. This also provides good 'tools' for heat production.

Surprisingly, activation of the TGR5 pathway not only promoted the expression of UCP1 in inguinal WAT, but also increased the expression of mitochondrial creatine kinase 2 (CKMT2)[116]. CKMT2 belongs to a subtype of creatine kinases and is another important factor in fat thermogenesis. CKMT2 regulates the futile creatine cycle (FCC) for heat production and promotes the energy consumption of beige adipose tissue and BAT, making it another mechanism of thermogenesis coexisting with UCP1-dependent thermogenesis[117,118]. It has been reported in early studies that creatine kinase (CK) is regulated by protein kinases such as PKA[119,120], and this view seems to provide a basis for the TGR5−cAMP−PKA−CKMT2 pathway to promote inguinal WAT browning. However, the detailed mechanism of TGR5−CKMT2, which induces thermogenesis, has not been fully studied. The latest research shows that tissue-nonspecific alkaline phosphatase (TNAP) initiates the FCC in thermogenic adipocytes[121] and that TNAP, CK and G-protein-coupled receptors have certain connections[122], which represent a hypothesis to be confirmed, that is, there may be upstream and downstream regulation between TNAP, CK and TGR5.

Furthermore, the heat production of mitochondria requires oxidizing substrates. Fatty acids (FAs), derived from the decomposition of lipids, are one of the substrates needed for mitochondrial oxidation. Among the different substrates of mitochondrial respiration, the most effective way to produce ATP is FA β oxidation[123], which means that UCP1 releases more heat in the process of FA β oxidation, thus achieving an obesity intervention effect. cAMP-dependent PKA coordinates the activation of lipolytic machinery through a hormone/phosphate-dependent mechanism[124]. In studies of TGR5 agonists, notoginsenoside Ft1 was found to promote lipolysis and thermogenesis in adipose tissue. This function mainly depends on the efficient induction of lipolysis in inguinal WAT by the TGR5−cAMP−PKA pathway. TGR5 significantly increases the protein level of PKA substrates. In the case of high expression of PKA, hormone-sensitive triglyceride lipase (HSL) is phosphorylated and moves from the cytoplasm to the surface of lipid droplets, promoting the hydrolysis of triglycerides and providing FA for mitochondrial β oxidation[125,126].

In summary, TGR5 can promote mitochondrial division, improve mitochondrial function and increase the expression of thermogenic genes. At the same time, TGR5 promotes the decomposition of lipids and provides enough FA substrates for mitochondrial β oxidation. TGR5 can effectively promote the browning of WAT from two aspects, namely, 'tool and fuel', to improve energy consumption and achieve weight loss (Fig. 5).

5.3. *TGR5 plays a role in appetite regulation*

In the mediobasal hypothalamus, there is a hypothalamic nucleus called the arcuate nucleus (ARC), and this neuronal circuit plays an important role in regulating energy consumption, heat production and food intake[127]. Recently, TGR5 was found to be expressed in the central nervous system (CNS), including the ARC[128]. Moreover, BAs were also found in the brain[129]. BAs can activate TGR5 to improve metabolism and promote anti-obesity, and whether TGR5 in the CNS is related to the anti-obesity effect was investigated experimentally. Fénelon et al.[130] demonstrated that acute intracerebroventricular injection of 3-(2-chlorophenyl)-*N*-(4-chlorophenyl)-*N*,5-dimethyl-4-isoxazolyl formamide (CCDC) or a BA mixture can activate TGR5 in the CNS. Subsequently, the body weight and food intake of obese mice were reduced, and insulin sensitivity and energy consumption were increased.

In the ARC area, there are regulatory neurons involved in food intake and coordination of satiety, including neuropeptide Y (NPY), agouti-related neuropeptide (AGRP), proopiomelanocortin (POMC), and cocaine- and amphetamine-regulated transcript (CART). Among them, ablation of NPY and AGRP neurons can lead to anorexia, weight loss and starvation, while ablation of POMC and CART neurons causes the opposite. Importantly, the promotion of appetite by AGRP/NPY neurons and the inhibition of appetite by POMC neurons have been confirmed in further

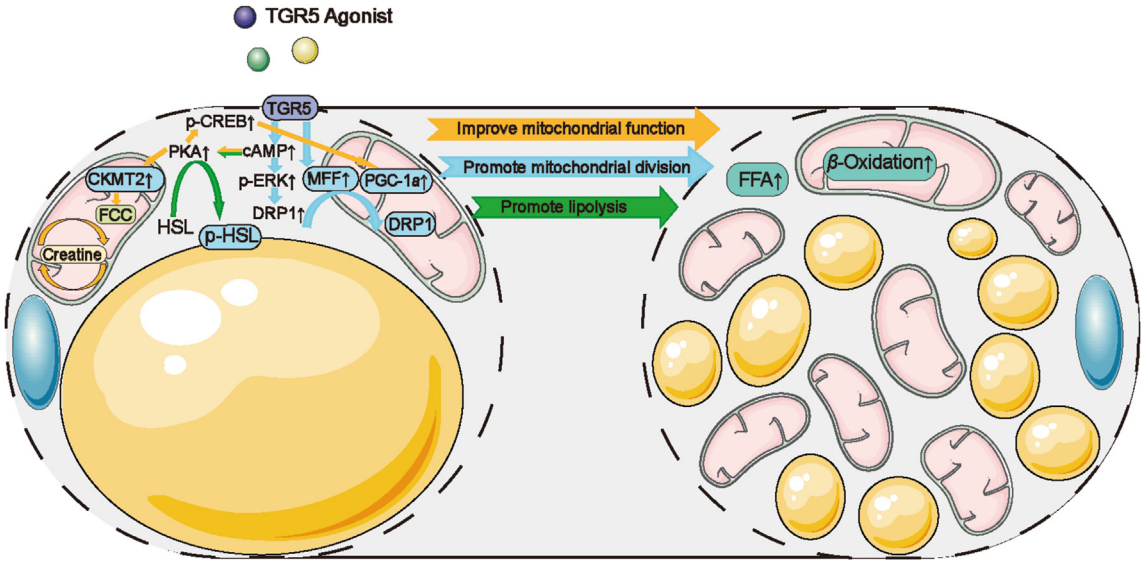


Figure 5 TGR5 promoting browning of white adipocytes.

studies[131]. Perino et al.[132] fully discussed the mechanism of TGR5 in controlling appetite in the CNS. In their study, it was found that although the activation of TGR5 did not affect POMC neurons, it could inhibit AGRP/NPY neurons under the activation of INT-777, effectively inhibiting the appetite of experimental mice without affecting the number of AGRP/NPY neurons. In further experiments, it was shown that the inhibition of AGRP/NPY after TGR5 activation occurs through the downstream Rashomologue/Rho-associated kinase (Rho/ROCK) signalling pathway. The reason is that the neuropeptides in AGRP and NPY are stored in dense-core vesicles (DCVs)[133], and the secretion of AGRP and NPY neuropeptides in DCVs is limited by the actin network[134], but the activation of the Rho/ROCK signalling pathway can stabilize actin and block the exocytosis of DCVs[135]. The normal energy balance in the body can self-regulate and maintain stability, which is does not necessarily occur through the regulation of TGR5. However, if the balance is upset in the state of obesity, TGR5 may be a good target.

TGR5 also regulates diet by promoting the secretion of gastrointestinal hormones, including PYY and GLP-1 secreted by intestinal L cells[136]. PYY_{3-36} and GLP-1 play a role in suppressing appetite. PYY_{3-36} and GLP-1 bind to neuropeptide Y receptor type 2 (Y2) and GLP-1 receptor (GLP-1R) on the vagus nerve, respectively, to transmit signals up to the nucleus tractus solitaries, which in turn transmit signals to the ARC. Thus, POMC neurons are activated and NPY/AGRP neurons are inhibited, effectively inhibiting appetite. In addition to the transmission of intestinal nerve signals, GLP-1 and PYY_{3-36} can also enter the blood from the intestinal tract, reach the ARC through the blood circulation pathway, and bind to the corresponding receptors to inhibit diet[137–140]. Furthermore, GLP-1 and PYY in the gut also stimulate satiety by delaying gastric emptying[141].

In addition, the intestinal peptide cholecystokinin (CCK) can induce satiety, and this effect is mediated by cholecystokinin A receptors (CCK-ARs) on vagal afferent neurons[142]. Interestingly, a study showed that TGR5 exists in nodose ganglia and coexists with CCK-ARs in a subpopulation of vagal sensory neurons. Under the activation of DCA and CCK-8, TGR5 and CCK-ARs cooperatively induced POMC and CART satiety neurons in the ARC, which inhibited food intake and reduced appetite signals[143]. The brain is the most complex and sophisticated organ of the human body. There is no complete and clear mechanism for the regulation of appetite by TGR5 expressed in the brain. In addition to the appetite control effects of TGR5 mentioned above, there are many factors involved in food intake, and whether these factors are related to TGR5 remains to be further studied (Fig. 6).

5.4. TGR5 regulates blood glucose homeostasis and improves insulin resistance

Obesity is associated with the pathogenesis of T2DM and is considered to be a contributing factor to T2DM[144,145]. Blood glucose homeostasis and energy imbalance are involved in both conditions. GLP-1, which belongs to the intestinal proinsulin family, was discovered in 1987. It is secreted by the intestinal tract and stimulates the GLP-1R. GLP-1 can effectively reduce blood glucose and help with weight loss by inhibiting the secretion of glucagon by pancreatic α cells and inducing pancreatic β cells to release insulin in a glucose-dependent manner[146–148]. An experiment showed that TGR5 is expressed on intestinal L cells, and TGR5 receptor agonists can effectively promote the induction of GLP-1 release[149]. The increase in GLP-1 secretion can effectively regulate glucose levels, lipometabolism and inflammation[150] and plays an essential role in maintaining glucose homeostasis and improving insulin resistance[151,152].

Recently, it was found that sleeve gastrectomy can increase the content of LCA in the portal vein, thus stimulating vitamin D receptor in the liver, inducing the expression of sulfonyltransferase, and promoting the synthesis and secretion of CA7S, a localized intestinal TGR5 agonist. CA7S can effectively promote the activation of TGR5 to increase the secretion of GLP-1 but can also increase the expression of TGR5[51,153]. This means that LCA can not only effectively promote the activation of TGR5 but can also indirectly promote the production of the endogenous TGR5 agonist CA7S.

Moreover, we found an interesting mechanism in our research. Previous studies have shown that the activation of FXR receptors in L cells interferes with glucose-dependent carbohydrate response

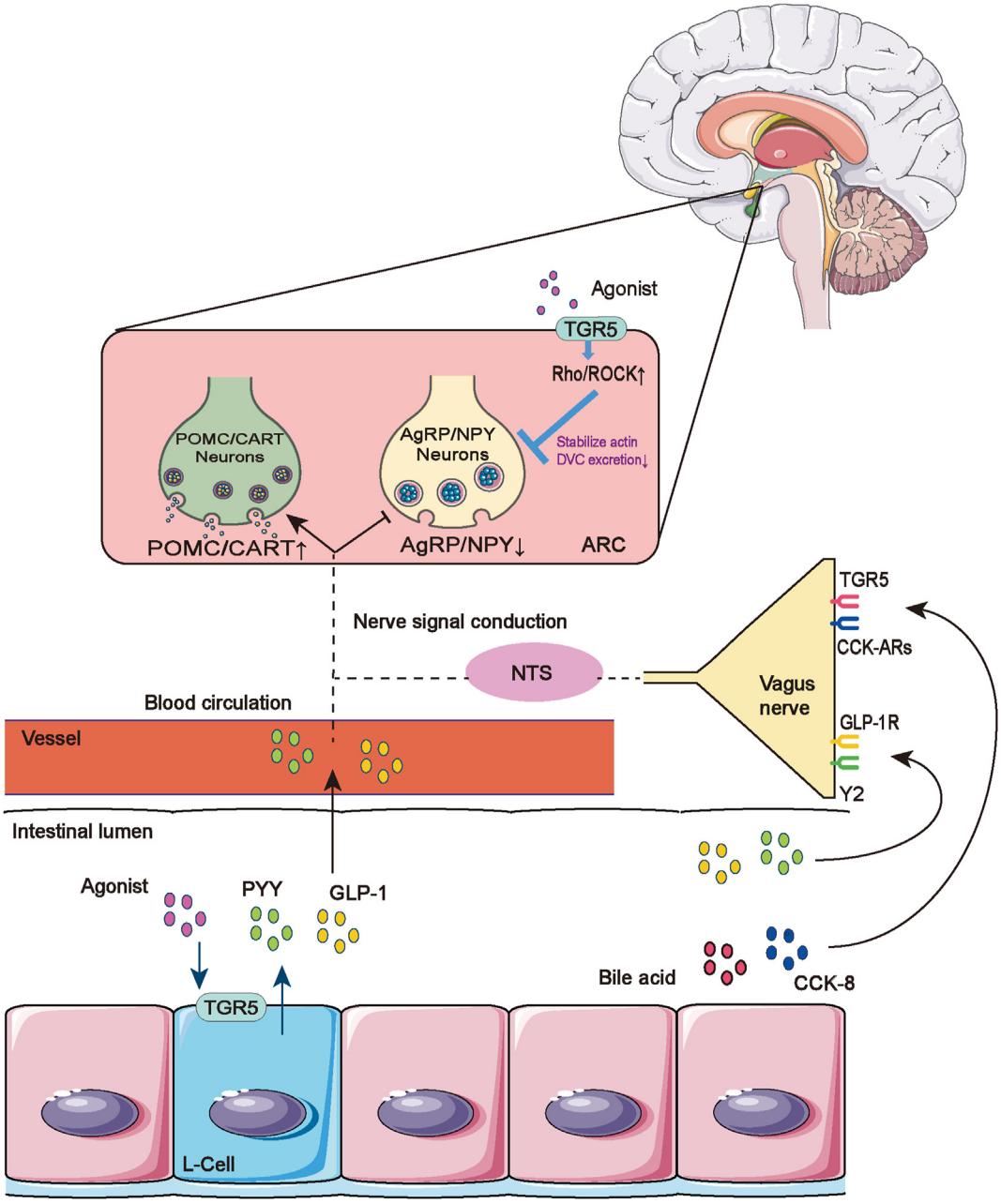


Figure 6 TGR5 controls appetite and regulates satiety.

element binding protein, reducing glycolysis and ATP production, thereby reducing glucose-responsive proglucagon transcription and GLP-1 secretion. In addition, FXR can also inhibit the signal transduction related to free fatty acid receptor 2-Gαq and the resulting GLP-1 secretion of short-chain fatty acids[154,155]. However, some studies have shown that crosstalk between FXR and TGR5 stimulates the secretion of GLP-1[156]. In intestinal L cells coexpressing FXR/TGR5, it was found that the FXR agonist Fexaramine could promote the intestinal restricted activation of FXR and induce *TGR5* gene transcription through the FXR binding site in the promoter of the *TGR5* gene[14]. In addition, the activation of intestinal FXR shapes the intestinal microflora and induces the reproduction of the LCA-producing bacteria *Acetatifactor* and *Bacteroides*[157]. This response can effectively promote the activation of TGR5 and increase the secretion of GLP-1 in intestinal L cells to improve the metabolism of TGR5[158,159].

Moreover, TGR5 not only promotes the secretion of GLP-1 in intestinal L cells but also regulates blood sugar by regulating islet cells. For islet β cells, the TGR5 receptor on its surface can promote the proliferation of islet β cells through the PKA−CREB pathway and increase insulin secretion in a glucose-dependent manner[160]. For islet α cells, TGR5 can induce the synthesis of GLP-1 through the PKA−CREB pathway. Glucagon and GLP-1 come from the enzymatic hydrolysis of proglucagon by proconvertase 2 (PC2) and proconvertase 1 (PC1), respectively. Activation of TGR5 induces PC1 activation, induces a shift from insulin synthesis to GLP-1 synthesis in α cells, and improves β cell function in a paracrine manner[161].

Insulin resistance is another hazard of obesity[162]. In individuals with obesity, the lipolysis reaction in hypertrophic adipose tissue produces an excess of free fatty acids (FFAs), which leads to impairment in β cell function and insulin resistance[163]. Excess FFAs can promote mitochondrial damage and tissue inflammation by increasing reactive oxygen species (ROS) levels and lipid peroxidation[164]. As mentioned above, TGR5 can effectively improve mitochondrial function and promote the oxidation of fatty acids, which largely alleviates the accumulation of excessive FFAs. In addition, TGR5 regulates the dynamic balance of blood glucose in skeletal muscle. When activated, TGR5 on skeletal muscle not only stimulates protein synthesis and muscle hypertrophy through the known insulin-like growth factor-1 (IGF-1)/phosphatidylinositol-3-kinase (PI3K)/protein kinase B (AKT) pathway[165] but also effectively promotes mitochondrial biogenesis by promoting the expression of PGC-1α[166]. In addition, the activation of TGR5 promoted the respiratory exchange ratio and increased the expression of phosphofructokinase. The latter promotes an increase in glycolytic flux and promotes glucose uptake and metabolism in skeletal muscle. That is, TGR5 regulates blood glucose balance by increasing blood glucose clearance in skeletal muscle and effectively improves muscle insulin resistance[167,168]. GLP-1 induced by TGR5 also improves insulin resistance in skeletal muscle. Under the action of GLP-1, GLP-1R in skeletal muscle can activate the cAMP/PKA pathway, induce the expression of Sirtuin1 (SIRT1), effectively promote the translocation of glucose transporter type 4 (GLUT4), and improve glucose uptake. Simultaneously, GLP-1 can improve the enhancement of insulin signalling pathway-related proteins, such as phosphorylated insulin receptor substrate 1 (IRS1) and phosphorylated AKT[61,169]. Furthermore, GLP-1 can promote the expression of the glycogen synthesis gene glycogen synthase 1/2 (GYS1/2) by promoting AMPK phosphorylation, and may also affect the translocation of GLUT4 to the cell membrane[170,171]. Furthermore, GLP-1 analogues can promote autophagy by regulating Sestrin2 (SESN2) in skeletal muscle cells, promote the expression of GLUT4 and effectively increase glucose uptake[172] (Fig. 7).

5.5. *TGR5 effectively improves inflammation and induces the M2 phenotype of macrophages*

Obesity is considered a class of chronic inflammatory diseases, including inflammatory macrophage infiltration and adipose tissue inflammation[173]. Macrophages have two phenotypes, M1 and M2. The activation of M1 macrophages can produce inflammatory factors, such as interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α), and the inflammatory inhibition of M2 macrophages is achieved by increased secretion of the anti-inflammatory cytokine interleukin-10 (IL-10)[174]. Insulin resistance in obesity is due to the accumulation of M1 macrophages[175].

TGR5 inhibits nuclear factor-kappa B (NF-κB) signal transduction and the activation of the NLRP3 inflammatory body[176] to reduce the expression of inflammatory factors such as TNF-α, IL-6, and IL-1β and activate NF-E2 p45-related factor 2/heme

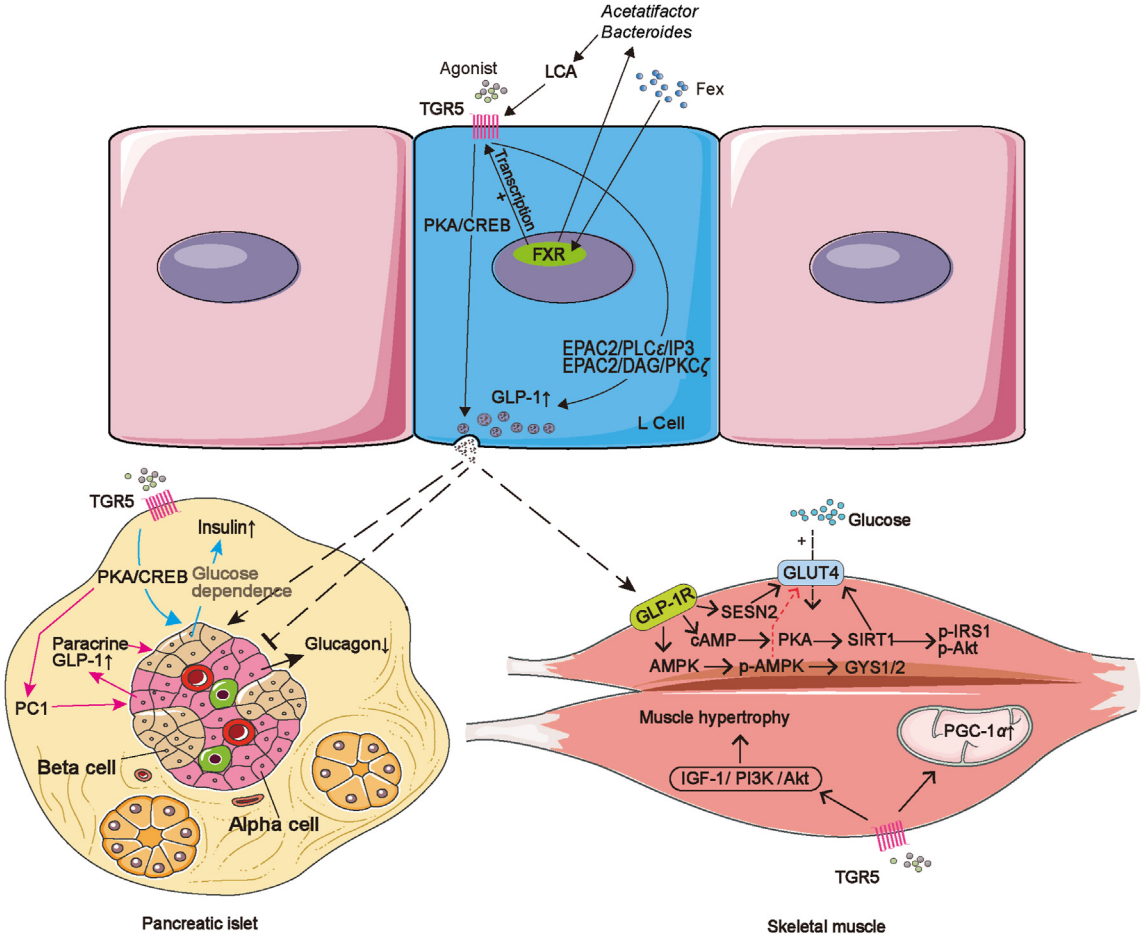


Figure 7 TGR5 effectively maintains blood glucose balance and improves insulin resistance.

oxygenase-1 (NRF2/HO-1) signal transduction, thus inhibiting the polarization of M1 macrophages and the production of ROS. At the same time, TGR5 agonists stimulated the expression of IL-10 and transforming growth factor-β (TGF-β), promoting the polarization of M2 macrophages[177–180]. Among them, the TGR5−PKA pathway increased the expression of c-FOS and increased its binding to p65, thus inhibiting the synthesis of NF-κB[181]. Additionally, TGR5−PKA pathway, its activation can promote the phosphorylation of CREB[182], enhance the ability to compete with NF-κB for CREB binding protein, and promote the secretion of IL-10 and TGF-β[178]. On the other hand, TGR5 can upregulate the expression of the CCAAT/enhancer binding protein β (C/EBP β) subtype LIP through the AKT-mammalian target of rapamycin complex 1 (mTORC1) signalling pathway in macrophages, which can inhibit the expression of the proinflammatory transcription factor liver activating protein (LAP), reduce the expression of chemokines in macrophages and reduce the infiltration of adipose tissue macrophages (ATMs)[183]. It was further shown that the activation of TGR5 could inhibit the expression of phosphorylated NF-kappa-B inhibitor alpha (IκBα) and the translocation of p65 and could weaken the DNA binding activity and transcriptional activity of NF-κB. At the same time, TGR5 also inhibits the NF-κB pathway by promoting the interaction between IκBα and β-arrestin2[184]. Moreover, TGR5 inhibited the expression of cathepsin E (Cat E) and promoted M2 macrophage polarization[174]. The above mechanisms also play a role in improving inflammation. Coincidentally, a growing body of research suggests that GLP-1 has anti-inflammatory effects[185]. As reported in a previous study, GLP-1 can reduce the infiltration of ATMs and effectively inhibit the activation of the macrophage NF-κB pathway by activating the cAMP/PKA signalling pathway. Additionally, it reduced the formation of the inflammatory factors TNF-α, IL-6 and IL-1β and achieved anti-inflammatory effects[175]. Moreover, the GLP-1 analogue liraglutide can effectively inhibit inflammasome NOD-like receptor pyrin domain-containing protein 3 (NLRP3)[186] and increase Nrf2/HO-1 signalling pathway transduction. These effects help to protect against oxidative damage and regulate inflammation[187,188], thus achieving an anti-inflamm atory effect. We believe that TGR5 can effectively inhibit the occurrence of inflammation and improve insulin resistance in both direct and indirect ways (Fig. 8).

In addition, the crosstalk between adipose tissue dendritic cells and ATMs is also involved in the obesity-induced inflammatory response. However, the mechanism between the two is not fully understood[189]. The literature has shown that activation of the TGR5−cAMP pathway can induce the differentiation of monocytes into interleukin-12 (IL-12) low-secretion dendritic cells and can reduce the secretion of proinflammatory factors[190]. The activation of TGR5 can also inhibit the production of glutathione. This TGR5 activation generates and induces oxidative stress,

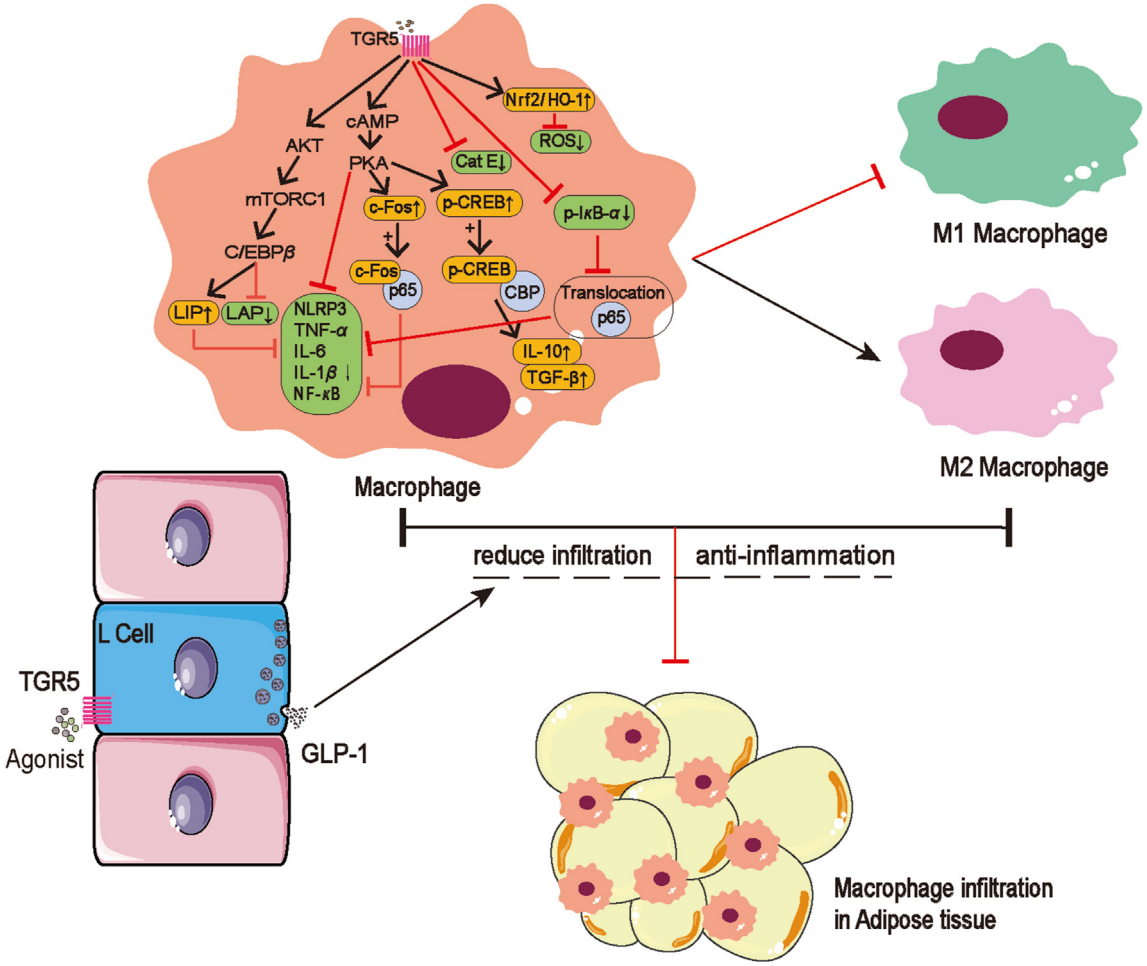


Figure 8 TGR5 inhibits the activation of inflammatory pathway and the secretion of inflammatory factors in macrophages through related pathways, induces M2 typing of macrophages, and effectively improves inflammatory response.

inhibits the NF-κB and MAPK pathways, and promotes autophagy and apoptosis of DCs[191,192]. TGR5 can also induce hepatic natural killer T (NKT)-biased NKT10 polarization and promote the secretion of IL-10 anti-inflammatory cytokines[193]. TGR5 additionally has a certain regulatory effect on the recruitment of T cells[194]. These results show that TGR5 has great potential to improve the chronic inflammatory response in obesity. The activation of TGR5 is not only anti-inflammatory but also effective in regulating the metabolism of the body.

6. Prospects

It is mentioned in this paper that superior mesenteric artery injection of DCA can effectively activate TGR5 receptors expressed in nodular ganglia, which cooperate with CCK-ARs activated by intestinal peptide CCK, thus affecting POMC and CART neurons in the hypothalamus and promoting satiety. Moreover, oral BAs or the agonist INT-777 can reach hypothalamic TGR5 within a certain period, stimulate TGR5-expressing neurons in the central nervous system, inhibit AGRP/NPY and reduce food intake. This information directly or indirectly suggests that TGR5 can control eating through the gut−brain axis. Notably, studies have shown that as the centre of food intake, thermoregulation and metabolism, there is a negative correlation in the hypothalamus between NPY and BAT activity. Knockout of NPY effectively promoted the expression of BAT in inguinal and interscapular fat, increased energy consumption, improved glucose homeostasis and enhanced insulin sensitivity[195,196]. By linking these data, we speculate that an as-yet undefined gut-brain-fat axis may be involved in the anti-obesity mechanism.

For clinical application, nuclear receptor FXR agonists are already available for clinical use, such as 6-ethylchenodeoxycholic acid for primary cholangitis and obeticholic acid for nonalcoholic steatohepatitis[197]. However, agonists of TGR5 are still lacking in the clinic, which may be related to the adverse effects of systemic activation of TGR5, such as inhibition of gallbladder emptying, pruritus, and reduction in systemic vascular resistance[198]. In recent research, many compounds have been shown to effectively activate TGR5. However, structural differences result in different titres and efficacies of TGR5 activation, and they may also promote/inhibit a variety of physiological and pathological activities *in vivo*. Perhaps from another perspective, on the basis of the full verification of the safety of compounds, it may be possible to explore TGR5 agonists in terms of titre and efficacy. In addition, TGR5 expressed in different locations plays different roles; for example, TGR5 on intestinal L cells activated by BAs can promote GLP-1 secretion; TGR5 on white adipocytes can promote browning; and TGR5 on brown adipocytes can promote thermogenesis. In view of this information, site-specific activation of TGR5 may reduce the harm caused by systemic activation.

7. Conclusions

When it was discovered that BAs played the role of signalling molecules, it at once aroused widespread concern in society. As a membrane receptor that receives BA signals, TGR5 has been proven to maintain glucose homeostasis and regulate energy metabolism. It mainly promotes the energy consumption of BAT to achieve the effect of weight loss. Moreover, BAs can activate central TGR5 expressed in the hypothalamus through the blood−brain barrier, which can effectively control appetite and reduce food intake. In addition, obesity is considered a chronic inflammatory disease, and TGR5 can effectively reduce the secretion of inflammatory factors by inhibiting M1 polarization of adipose tissue macrophages and promoting M2 polarization. The above results show that TGR5 is a very promising therapeutic target for obesity, and the successful research and development of TGR5 agonists will also provide a series of benefits in the future.

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Author contributions

Weijun Lun: Writing—Original Draft, Conceptualization, Visualization. Qihao Yan, Xinghua Guo, Minchuan Zhou: Investigation, Writing—Review & Editing. Yan Bai: Data Curation. Jincan He, Qishi Che: Resources. Hua Cao: Data Curation. Jiao Guo, Zhengquan Su: Funding acquisition, Project administration.

Conflicts of interest

The authors declare no conflicts of interest.

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