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# Plin5: A potential therapeutic target for type 2 diabetes mellitus

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**Abstract**
Type 2 diabetes mellitus (T2DM) is a kind of metabolic disease characterized by aberrant insulin secretion as a result of -cell loss or injury, or by impaired insulin sensitivity of peripheral tissues, which finally results in insulin resistance and a disturbance of glucose and lipid metabolism. Among them, lipid metabolism disorders lead to lipotoxicity through oxidative stress and inflammatory response, destroying the structure and function of tissues and cells. Abnormal lipid metabolism can lead to abnormal insulin signaling and disrupt glucose metabolism through a variety of pathways. Therefore, emphasizing lipid metabolism may be a crucial step in the prevention and treatment of T2DM. Plin5 is a lipid droplet surface protein, which can bi-directionally regulate lipid metabolism and plays an important role in lipolysis and fat synthesis. Plin5 can simultaneously decrease the buildup of free fatty acids in the cytoplasm, improve mitochondrial uptake of free fatty acids, speed up fatty acid oxidation through lipid drops-mitochondria interaction, and lessen lipotoxicity. In oxidative tissues like the heart, liver, and skeletal muscle, Plin5 is extensively expressed. And Plin5 is widely involved in β-cell apoptosis, insulin resistance, oxidative stress, inflammatory response and other pathological processes, which has important implications for exploring the pathogenesis of T2DM. In addition, recent studies have found that Plin5 is also closely related to T2DM and cancer, which provides a new perspective for exploring the relationship between T2DM and cancer.

**Keywords** Plin5, Lipid droplets, Type 2 diabetes mellitus, Lipid metabolism

## Introduction

Glucose homeostasis is coordinated by basal and postprandial insulin secretion on the one hand and is also influenced by free fatty acid levels on the other. The elevation of circulating fatty acids during fasting accelerates the consumption of fatty acids and releases a large number of fatty acid metabolites by activating G protein-coupled receptor 40 (GPR40) on the cell surface [1, 2], leading to an acute increase in insulin release to maintain postprandial insulin requirement [3, 4]. Normally, excess fatty acids in the body are stored in lipid droplets by white adipose tissue in the form of neutral lipids, such as triglycerides, for a rainy day. Interestingly, the consumption of fatty acids during fasting impairs subsequent insulin secretion [5], which may be related to the large production of fatty acid intermediates. Excess lipid "spills" into non-adipose tissues such bone and cardiac muscle, liver, and pancreas, also known as "ectopic fat," when a significant amount of lipid accumulates when the intake exceeds the storage capacity of adipose tissue. Numerous studies have shown that it is not the fatty acids themselves that play a negative role in insulin response or hormone secretion, but some of their lipid derivatives, such as diglycerides and/or ceramides [6–8]. Ectopic fat is thought to promote and/or worsen tissue

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insulin resistance and lipotoxicity, which results in tissue dysfunction [9].

Plin5 is a lipid droplet surface protein whose abundance in humans predicts insulin sensitivity [10]. Plin5 has a high level of expression in oxidized tissues such the heart, skeletal muscle, and brown adipose tissue, and it is increased in the liver and heart during fasting [11–13]. Human insulin resistance and lipotoxicity may be modulated by Plin5 alteration of intracellular lipid droplets, according to preliminary research [14]. Plin5 can control the lipid metabolism of oxidative tissues in both directions [15], in addition to taking role in the control of insulin secretion [16]. Plin5 may be a viable intervention target for the treatment of T2DM patients as a result of its distinct regulatory role.

Loss of a functional β-cell population is a fundamental defect in diabetes [17]. It has been proposed that Plin5 helps postprandial insulin secretion by regulating intracellular lipid metabolism in β cells [16]. Specifically, the increase in islet Plin5 during fasting enables the breakdown of fatty acids into lipid droplets, which are released upon refeeding and support postprandial insulin production in a cAMP- and GPR40-dependent manner [16]. Postprandial hyperglycemia is an early defect of T2DM and a major barrier to achieving optimal glycemic control in diabetic patients [18–20]. This regulatory function of Plin5 serves as a link between the control of lipid and glucose metabolism and offers a possible target for therapeutic intervention in the control of postprandial blood glucose. Moreover, Plin5 can enhance the effectiveness of fatty acid metabolism, protect cells from oxidative stress damage, and stimulate the transfer of fatty acids from lipid droplets to mitochondria through the contact mechanism of lipid droplets and mitochondria [21, 22]. The regulation of Plin5 on glucose and lipid metabolism is of great significance for exploring the pathogenesis and clinical intervention direction of T2DM. In order to investigate the therapeutic value of Plin5 in T2DM, we therefore analyzed and discussed the molecular mechanism of Plin5 in regulating glucose and lipid metabolism in T2DM patients, summarized the drug interventions and the most recent research advances targeting Plin5 and related pathways, and objectively analyzed the research value and disadvantages.

## Molecular mechanism

### Transcriptional regulation of Plin5

Plin5 (Periilipin-5, LSDA5, LSDP5, MLDP, OXPAT) belongs to the family of domains called PAT [23] and is a phosphorylated protein and is involved in hormone-stimulated lipolysis [24, 25]. Plin5 transcripts were most prevalent in the heart, followed by skeletal muscle and liver [13]. Plin5 is localized at multiple locations within the cell, including lipid droplets, endoplasmic reticulum, mitochondria, and cytoplasm [26], and may regulate the dynamic interaction between lipid droplets and mitochondria, which is thought to be involved in the etiology and treatment of insulin resistance [10, 27]. Recent studies have found that Plin5 derived from neural stem cells can regulate lipid metabolism homeostasis and promote bone regeneration through endocrine regulation driven by brain-skeleton axis [28], which provides a basis for the development of drugs targeting lipid or bone regeneration.

Peroxisome proliferator-activated receptors (PPARs), ligand-activated transcription factors belonging to the nuclear receptor superfamily, control the expression of the plin5 gene. They control gene transcription by interacting with peroxisome proliferative response elements via heterodimerization with retinoid X receptors [29]. PPARα plays a key role in stimulating fatty acid oxidation during fasting [24, 30]. Lipid droplet function depends on the production of certain nuclear transcription factors of the PPAR family [31–33], which are then activated by ligands produced by lipid droplet catabolic function [34–37], a feedforward cycle. Therefore, lipid droplets may reduce lipotoxicity by regulating PPAR nuclear activity and promoting increased fatty acid flux through the mitochondrial oxidative pathway [38]. PPAR ligands are being employed in the clinical treatment of obesity, diabetes, and hyperlipidemia, but it is not entirely understood how their therapeutic effect is mediated at the molecular level. When plin5 is not controlled by PPAR, Plin5 mutation can increase the risk of cancer, such as breast cancer [39] and gastric cancer [40].

The expression control of Plin5, in addition to being affected by free fatty acids, is also regulated by other factors, such as leptin [41] and lipin-2 [42]. Among them, leptin can reduce the N(6) -methyladenosine (m(6)A) methylation of Plin5 and regulate lipolysis by promoting obesity-related genes [41]. Ovarian cancer may advance if Plin5 is methylated, while demethylating Plin5 can stop ovarian cancer cells from proliferating, migrating, and invading while increasing apoptosis [43]. Therefore, while regulating plin5 to improve lipid metabolism, attention should be paid to the gene mutation and methylation of Plin5 to prevent carcinogenesis.

### Plin5 and lipolysis

In the fed state, Plin5 expression is very low, and both mRNA and protein levels of Plin5 increase during fasting [16]. This phenomenon has been confirmed in observational studies of heart, liver and islet cells [16, 44]. Early studies highlighted the role of Plin5 as a lipid barrier [22]. The multiple functions of Plin5 may be conferred through its interaction with ATGL and ABHD5 [45–47] and its ability to increase lipolysis through PKA stimulation [47].

Plin5 increases lipolysis in response to PKA activation [47] and can amplify the effects of PKA and cAMP signaling pathways on insulin secretion [16]. After cAMP/PKA-mediated lipid stimulation, plin5 preferentially binds monounsaturated fatty acids from lipid droplets and transports them to the nucleus. In cellular and animal models, monounsaturated fatty acids boost PGC-1/PPAR signaling, allosterically activate sirt1 toward specific peptide substrates like PGC-1, and encourage oxidative metabolism in a SIRT1-dependent way [48]. Plin5 controls lipid consumption and accumulation by regulating phosphorylation [49]. The prevailing view on lipolysis is that: (1)ATGL and ABHD5 interact with PLIN5 on lipid droplets, respectively, promoting their interaction and driving lipolysis [45, 46]; Or (2)Plin5 and ABHD5 each recruit ATGL to lipid droplets, with opposite effects; ABHD5-ATGL interaction promotes lipolysis, and Plin5 binds to ATGL to inhibit lipolysis [11, 47]. Plin5, which is located on the outer membrane of mitochondria and can link lipid droplets to mitochondria [50], can well guide fatty acid oxidation [51, 52], and regulate fatty acid supply through feedback inhibition that may involve ABHD5, ATGL and HSL [52, 53], optimizing oxidation efficiency to buffer excess fatty acids.

Plin5 is essential for both fatty acid oxidation and mitochondrial function, which is achieved through lipid drop-mitochondrial contact [54]. The overexpression of Plin5 can promote the formation of lipid droplets and mitochondrial-lipid droplet contact, reduce the level of ROS in cells, up-regulate COX and CS and other mitochondrial function-related genes [55], and effectively protect mitochondrial function. However, inhibition of Plin5 showed the opposite effect [55]. When Plin5 is lacking, mitochondrial function and membrane depolarization are significantly impaired and mitochondrial oxidative capacity is weakened in mouse hearts [56]. Thus, Plin5 expression is indispensable for the maintenance of mitochondrial function. Another study found that Plin5-s155a is considered a prerequisite for stimulating lipolysis and may play a key role in preserving cardiac function. The heart of Plin5-s155a mice showed reduced fatty acid oxidation but normal ATP [57]. Interestingly, mitochondrial recruitment of dynamin-related protein 1 (Drp1) was significantly reduced in the myocardium of Plin5-s155a and Plin5 transgenic mice, along with reduced phosphorylation of mitochondrial fission factor (the mitochondrial receptor for Drp1) [57]. This suggests that Plin5 may be involved in the inhibition of mitophagy, and once again confirms the close relationship between plin5 and mitochondria.

#### Plin5-associated chaperone protein

ATGL and ABHD5 are the main chaperone proteins of Plin5, which synergically regulate the decomposition and synthesis of lipid droplets in the contact between lipid droplets and mitochondria. In order to fully understand the biological role of Plin5, we discussed its interaction with chaperone proteins. ATGL is responsible for the first and rate-limiting step of triacylglycerol hydrolysis in adipocytes, skeletal muscle, and heart. Loss of islet-targeted ATGL leads to widespread impairment of insulin secretion through impairment of mitochondrial respiration [58] and can also lead to cardiac steatosis, severe cardiomyopathy, and premature death [35]. However, adipose tissue-specific overexpression of ATGL can improve the metabolic status of mice fed a high-fat diet [59]. These evidences demonstrate the essential role of ATGL in lipid metabolism. HSL is a lipase that is highly specific for diacylglycerol and appears to have complex effects on insulin secretion, as conflicting phenotypes have been reported in mouse models of HSL regulation [2, 60].

ABHD5 (CGI-58) is a key upstream regulator of ATGL and can effectively increase the activity of ATGL and other lipases [61, 62]. In tissue cells such as skeletal muscle and heart, Plin5 binds ABHD5 and inhibits both basal and stimulated lipolysis [12, 63]. At present, the regulatory mechanism of Plin5 on ABHD5 is not clear, but both of them have shown potential therapeutic value in cancer-related fields. ABHD5 has recently been shown to be a potent tumor suppressor in colorectal cancer [64], and its ligand can bypass typical PKA-dependent signaling [65] and stimulate lipolysis in adipocytes and muscle to delay or prevent tumor progression by promoting oxidative metabolism [65]. As one of the fatty acid metabolism genes, Plin5 expression is significantly different and significantly down-regulated in breast cancer [39], which can be used as a biomarker and potential therapeutic target for poor prognosis of breast cancer. The above studies show that Plin5 and ABHD5 not only provide a basis for the development of new lipolysis regulators, but also build a bridge for the study of metabolic diseases and tumors, and strengthen the connection between different diseases.

#### The role of Plin5 in T2DM

More and more studies have found that Plin5 plays an important role in the protection of multiple damaged target organs in T2DM. The overexpression or deletion of Plin5 can lead to metabolic abnormalities of related tissues and cells, and even regulate the pathological processes such as apoptosis and tissue damage. Therefore, in this part, we focus on the regulatory effects of Plin5 on different damaged target organs of T2DM, just as Table 1, in order to explore potential intervention targets and signaling pathways, and provide ideas for clinical intervention.

**Table 1** The roles of Plin5 in diabetes-related target organs

| | Plin5 status | pathway | changed | Reference |
|---|---|---|---|---|
| Fat | Plin5 phosphorylation | Cold stimulates lipolysis↑ | Browning of white fat cells↑ | [49, 66] |
| skeletal muscle | Plin5 expression | Lipid droplet decomposition and synthesis | insulin sensitivity↑ | [67] |
| liver | Plin5 deficiency | JNK-p38-ATF pathway | Impaired insulin signal transduction↑ | [55, 68] |
| pancreas | Plin5 overexpression | PI3K/Akt pathway↑, ERK pathway↑ | apoptosis↓, oxidative stress↓, Lipotoxicity of β-cells↓ | [69, 70] |
| heart | MHC-Plin5 mice | Plin5 interacted with SERCA2↑, calcium treatment↑ | Myocyte contractility↑, Left ventricular mass and myocardial cell size↑, Heart function is preserved | [71] |
| sertoli cell | Plin5 overexpression | Akt/GSK-3β/ NRF2 pathway↑ | Apoptosis↓, Oxidative stress and inflammation↓, sertoli cell injury↓ | [72] |
| blood vessel | ApoE$^{(-/-)}$Plin5(-/-) | PI3K/AKT and MAPKs pathway↑, NF-κB pathway↑ | Oxidative stress and inflammation↑, Lesion of capillary structure and function↑ | [73, 74] |

### Browning of white fat cells

Lipids are stored in white adipose tissue as an energy reserve and released into the bloodstream as needed. Instead, brown adipose tissue produces heat by oxidizing stored fatty acids in order to regulate body temperature [75]. White adipocytes normally contain a single large lipid droplet that takes up most of the cytoplasm, whereas brown adipocytes, which are mitochondrial-rich, are loaded with numerous smaller lipid droplets, reflecting their diverse activities. The recent discovery of adult brown adipose tissue has sparked investigation into its possible use in the management of obesity or T2DM [76, 77]. Browning of white adipocytes is a particularly promising strategy.

When exposed to cold, mice's brown adipose tissue's levels of the lipid droplet protein Plin5 drastically rise [78]. Enhancing Plin5 activity in brown adipose tissue is crucial for diet-induced hepatic steatosis, improving systemic glucose tolerance, and healthy remodeling of subcutaneous white adipose tissue. In adipocytes, peripheral phospholipids protect lipid droplets from lipase under basal conditions. Plin5 is phosphorylated by camp-dependent protein kinase A in response to hormonal stimulation, and this causes the recruitment of hormone-sensitive lipases and other lipases to lipid droplets, which encourages lipolysis [49, 66]. Fatty acids are necessary and sufficient for thermogenesis in brown adipocytes [79–81]. White adipocytes respond to external signal output to mobilize fatty acids, and other tissues, including muscle and brown adipose tissue, mobilize fatty acids from intracellular lipid droplets for in situ oxidation. Therefore, it can be expected that additional mechanisms exist to balance the supply and demand of fatty acids independent of transmembrane signaling.

In addition, adipose differentiation-related proteins (ADRP, also known as Plin2) are ubiquitally expressed and play a role in lipid incorporation and accumulation [82–85]. Since the expression level of Plin2 is highly dependent on the total mass of adipocytes [82, 86], it can be used as a marker of lipid storage and disease status in fat-accumulating cells [87, 88]. Plin2 overexpression stimulates fatty acid uptake and triglyceride formation in various cell types [85, 89]. The increase in lipolysis substrates and the accessibility of these lipases to triglyceride-loaded lipid droplets may primarily determine the rate of lipolysis [16]. It is yet unknown what separates "healthy" intracellular lipid accumulation from "lipotoxic" accumulation linked to islet dysfunction.

### Skeletal muscle insulin resistance

Plin5 is indispensable for normal substrate metabolism and skeletal muscle adaptation to exercise training [90]. Plin5 fine-modulates lipid oxidation to meet metabolic demands and protects skeletal muscle against lipotoxicity [91]. Skeletal muscle is an important site for postprandial glucose disposal [92]. When the excess supply of fatty acids exceeds the energy demand of muscle cells, skeletal muscle [93] fails to mobilize triglyceride fatty acids and/or increases triglyceride breakdown, leading to excessive intracellular lipid accumulation and insulin resistance [94, 95]. Independent of fat, accumulation of intracellular triacylglycerol predicts insulin resistance in muscle [96–99]. However, this link is unclear because athletes have the same amount of triglycerides in muscle as T2DM patients while still having excellent insulin sensitivity [100], a condition known as the "athlete paradox" [101, 102]. This could be related to a benign style of IMCL storage in athletes, defined by lipid storage in type I muscle fibers, ideally encapsulated with Plin5 in small and plentiful lipid droplets, without impairing insulin sensitivity [103]. However, some studies have pointed out that the abundance of Plin5 does not have a causal relationship with the athlete paradox [104]. It can be determined that in both athletes and T2DM patients, it is not fatty acids themselves that cause insulin resistance in muscles, but lipid derivatives such as DAG and ceramides (derived from saturated fatty acids such as palmitates) [6, 105].

Plin5 is extensively expressed in skeletal muscle [12], reduces skeletal muscle lipolysis, especially during extended food deprivation, has no effect on mitochondrial reprogramming, and maintains insulin sensitivity in skeletal muscle by inhibiting ceramide formation

[67]. Although triglyceride accumulation in muscle cells has been implicated in insulin resistance [96, 97], emerging data suggest that the etiology of insulin resistance is related to the uncoupling of lipolysis in muscle cells from the cellular requirement for fatty acids [93, 106]. Plin5 can be mildly overexpressed into rat glycosylated muscle by DNA electrotransfer, increasing triglyceride accumulation [21], which is consistent with the general consensus that Plin5 plays an important role in lipid droplet accumulation [11–13]. Although Plin5 increased triglyceride accumulation, this did not appear to have an effect on skeletal muscle insulin action [107].

Enlarged plin5 uncoated lipid droplets in the internal region of type II fibers of skeletal muscle are associated with T2DM [108]. Plin5 and Plin2 proteins are expressed in human and rat skeletal muscle in a fiber type-specific manner, with higher expression in fibers with higher lipid storage capacity [109]. Plin2 is expressed in skeletal muscle at both mRNA [31, 82] and protein [110, 111] levels. In the absence of neutral lipids, Plin5 is present in the cytoplasm and moves to lipid droplets under conditions that promote lipid droplet formation [12, 13]. Plin2 is destroyed by the proteasome if it is not attached to neutral lipids [112, 113]. It has been shown that insulin-stimulated glucose uptake is inversely correlated with Plin2 content [109] and suggests that low, rather than high, Plin5 and Plin2 content contribute to improved insulin sensitivity. Plin5 and Plin2 are widely involved in regulating muscle fat storage and degradation processes, affecting the level and type of lipid intermediates. Since lipid intermediates have been linked to skeletal muscle insulin resistance and the development of T2DM, Plin5 and Plin2 may be promising options for reducing skeletal muscle insulin resistance.

#### Inflammation in the liver

The separation between insulin resistance and accumulating lipid droplets is not restricted to muscle tissue, but has also been shown in mouse models [114] and in humans [115]. Plin5 is essential for the maintenance of mitochondrial-mediated adipogenesis. Plin5 deficiency reduces lipid droplet accumulation by increasing fatty acid outflow, which is associated with decreased hepatocyte lipogenesis and mitochondrial dysfunction [116]. Importantly, Plin5 deletion abolished the differences in mitochondrial oxidative capacity around lipid droplets and in the cytosol [116]. Recent studies have shown that cellular oxidative stress can up-regulate the expression of Plin5 through the JNK-p38-ATF pathway [55], which provides an important new perspective on the regulatory mechanism of Plin5 in lipid metabolism and oxidative stress in hepatocytes.

Plin5 plays a significant role in intrahepatic lipid metabolism [68]. On a high-fat diet, Plin5 knockout mice display c-Jun N-terminal kinase activation, impaired insulin signaling, and insulin resistance in the liver, impairing systemic insulin action and glycemic control [68]. However, these effects are reversed when Plin5 is re-expressed in the liver of Plin5 knockout mice [68]. This suggests that increased Plin5 expression during overnutrition may play an important role in the prevention of hepatic insulin resistance. However, contrary to this, some studies have proposed that blocking Plin5 may be a mechanism to improve hepatic glucose metabolism, and they found that Plin5 deficiency can improve obesity and glucose tolerance induced by high-fat diet, and reduce liver damage [117]. Moreover, Plin5-null mice have lower glucose production and insulin-sensitive gluconeogenic gene expression in the liver compared with muscle [67]. Although these two studies present different points, together they confirm that Plin5 deletion can lead to impaired insulin secretion. In addition, Plin5 signaling can also promote autophagy and prevent fatty acid-induced inflammation via SIRT1 as a means to maintain hepatocyte homeostasis during fasting and fatty acid mobilization [118]. Furthermore, muscle-liver interaction is crucial for controlling metabolic balance. Through altering lipid metabolism, Plin5 deletion decreased muscle ER stress, liver and muscle FGF21 synthesis, and blood glucose levels [119].

The liver receptor homolog-1 (LRH-1) controls the transcription of plin5, which in turn controls the metabolism of hepatic lipids, bile acids, and glucose. For the regulation of hepatic lipid metabolism and glycemic control, Plin5 s155 must be phosphorylated by PKA [120]. Liver receptor homolog-1 binds to the binding site of Plin5 promoter sequence-1620/-1614 [121] and promotes the expression of plin5. When liver receptor homolog-1 is specifically knocked out in hepatocytes, Plin5 expression and β-oxidation related genes are reduced, and triglyceride in liver is significantly increased [121]. In order to mobilize lipid droplets, safeguard the liver from lipid overload, and control cellular demand during fasting, this suggests that Plin5 may be a novel target for liver receptor homolog-1. Moreover, Plin5 is also under the control of LCN2, a key regulator of hepatic lipid homeostasis [42]. Liver receptor homolog-1 and LCN2 may be potential intervention targets for regulating the expression of plin5 in hepatocytes. Intestinal flora also plays a key role in liver injury and lipid metabolism, among which Salmonella (harmful bacteria) can affect liver lipid metabolism by down-regulating Plin5 [122]. Therefore, the abnormal liver lipid metabolism mediated by gut microbiota through the gut-liver axis is also an intervention pathway that cannot be ignored.

### Pancreatic B cell injury

Inadequate pancreatic -cell activity and even apoptosis are hypothesized to result from prolonged exposure of pancreatic -cells to excessive free fatty acids. In the lipotoxic microenvironment induced by excessive fatty acids, the expression of metabolism-related gene plin5 is up-regulated, and the expression of genes related to pancreatic β cell function is decreased [70]. Up-regulation of Plin5 expression can reduce lipotoxicity of INS-1β cells and improve cell viability, apoptosis and β cell function [123], which may be achieved by enhancing fatty acid storage and reducing endoplasmic reticulum stress. Increased Plin5 expression during fasting provides a mechanistic basis for the previously documented contribution of fatty acids to subsequent insulin secretion during fasting [5], as Plin5 would allow β cells to store fatty acids during fasting and mobilize them to produce lipid signals to increase insulin secretion in response to refeeding cAMP [16].

Plin5 overexpression increases lipolysis in β cells [16], induces Nrf2-ARE system, the main regulator of cellular adaptive response to oxidative stress, and promotes the enhancement of antioxidant defense by activating PI3K/Akt and ERK signaling pathways, thereby improving the function and survival of β cells under lipotoxic oxidative stress [69]. In addition, gene silencing of activator protein 1 member JunD also regulates the function of pancreatic β cells by changing plin5 protein, regulating apoptosis and oxidative stress, and reversing lipotoxicity of β cells [70]. The increase in camp-dependent lipolysis mediated by Plin5 may be sufficient to alter the intracellular profile of lipid metabolites in β cells to regulate insulin secretion [16]. It appears that intracellular lipid metabolism and GPR40 signaling pathways are interwoven [124] rather than functioning as two distinct routes because GPR40 agonists increased lipolysis and fatty acid binding to diacylglycerol in islet cells. Further studies should be conducted to determine whether Plin5 itself is a molecular target of GPR40 signaling. Interestingly, upregulation of Plin5 expression may reduce the risk of pancreatic cancer. Recent studies have found that plin5 expression is down-regulated in pancreatic cancer, which is significantly related to the overall survival of pancreatic cancer patients [125]. Of note, although Plin5 is a differentially expressed gene in pancreatic cancer, it is not an independent predictor of pancreatic cancer. The role of Plin5 in pancreatic cancer remains to be further studied.

### Cardiac dysfunction

The capacity of cardiomyocytes to store triglycerides is rather limited, so the balance between fatty acid uptake, storage, and mitochondrial oxidation is tightly regulated [126]. TAG levels in myocardium are negatively correlated with cardiac function, and chronic lipid accumulation leads to cardiac dysfunction [127–129]. Plin5 is selectively expressed in the heart under normal conditions and when it is either PPARα or fasted, Plin5 may preferentially reside on lipid droplets in tissues with high rates of lipolysis, thereby promoting intracellular lipid depletion. Conversely, by activating PPARα, it raises the possibility that this PAT has the opposite function, namely lipid accumulation [13]. Overexpression or deletion of Plin5 beyond the physiological limit also resulted in cardiac damage. On the one hand, deletion of Plin5 reduced lipid droplet size [67] and increased fatty acid oxidation in the heart. This is due to increased ATGL-mediated TAG lipolysis and, independently, increased fatty acid oxidation capacity in cardiomyocytes [44]. On the other hand, PLIN5 overexpression in myocardium inhibited ATGL-mediated lipolysis and was associated with decreased mRNA content of oxidative phosphorylation protein, decreased mitochondrial enzyme activity, and mildly impaired mitochondrial respiration [130, 131]. This results in increased lipid droplet volume, myocardial steatosis, slightly impaired oxidative metabolism, and mild cardiac dysfunction [130, 131].

There are two main pathogenesis of cardiac dysfunction caused by T2DM. Increased oxidative stress brought on by increased mitochondrial ROS generation as a result of excessive fatty acid oxidation is one factor [132–134]. The other is the excessive buildup of lipotoxic lipid derivatives, like ceramides and diacylglycerol, which interfere with a number of signaling pathways, including the protein kinase C (PKC) pathway [135–137]. It is unclear which of these two factors most significantly contributes to the onset of diabetic cardiomyopathy, though. In the hearts of type 1 diabetic mice, Plin5 encourages excessive TAG accumulation, which is accompanied by an increase in lipotoxic lipid derivatives. These compounds then activate NOX2 through PKC signaling, which results in excessive ROS production and ultimately diabetic cardiomyopathy [138]. Yet, cardiac steatosis is unaffected in Plin5-null mice, and they display age-related cardiac dysfunction that can be avoided with antioxidant therapy [44].

Plin5 not only acts as an independent protective factor in acute coronary syndrome [139], but also shows a potential protective effect in myocardial hypertrophy [71]. In physiological condition, cardiomyocytes can reduce the pressure of the ventricular wall and compensate for cardiac hypertrophy when the load increases, which is beneficial to the protection of the heart. However, when the load of the heart exceeds its self-regulatory capacity, it will cause pathological myocardial hypertrophy, and even develop into heart failure. Recent research has revealed that cardiac Plin5 expression is linked to an increase of processes relevant to cardiac contraction, and that heart-specific Plin5 overexpression encourages

cardiac hypertrophy [71]. Cinato, M., et al. In mice with heart-specific Plin5 overexpression (MHC-Plin5 mice), it was shown that cardiac Plin5 interacted with SERCA2 to facilitate the handling of calcium, improve the contractility of cardiomyocytes, and increase left ventricular mass and size while maintaining cardiac function [71]. This suggests that cardiac hypertrophy caused by Plin5 overexpression may be a physiological protective effect. However, it has also been noted that Plin5 deficiency can exacerbate pressure overload-induced cardiac hypertrophy and heart failure [140] This may be due to an increase in PPAR and PGC-1 levels, which will encourage mitochondrial proliferation and enhance fatty acid utilization while decreasing lipid accumulation [140]. The relationship between the activation of other pathways and Plin5 under pressure overload is not clear, and whether the effect of Plin5 expression status on cardiac hypertrophy contributes to the adaptive protection of the heart remains to be further explored.

#### Plin5 and other related target cells

Plin5 plays a significant role in the oxidative stress and inflammation that occur during atherosclerosis. Recent research has revealed that Plin5 expression is elevated in the arteries of ApoE(-/-) mice. ApoE(-/-) mice exhibit increased numbers of inflammatory neutrophils and monocytes, as well as the overexpression of inflammatory cytokines and chemokines [73], and the NF-B pathway is substantially activated. Notably, ApoE(-/-) Plin5(-/-) significantly induced apoptosis and increased cleavage of Caspase-3 and PARP-2 [73]. In addition, ApoE(-/-) Plin5(-/-) promoted the generation of oxidative stress in aortic tissues, which was associated with the activation of PI3K/AKT and MAPKs pathways [73]. Intimal hyperplasia is characterized by aberrant vascular smooth muscle cell migration and proliferation in arterial arteries. Through interacting with PGC-1, Plin5, a powerful regulator of vascular smooth muscle cell proliferation, migration, and neointimal hyperplasia, prevents vascular smooth muscle cell proliferation and migration [141]. In addition, Plin5 also plays an important role in vascular endothelial cells. According to studies, Plin5 ablation and phosphorylation decrease lipid droplet content, boost intracellular FFAs, stimulate mitochondrial -oxidation, increase ROS production, decrease endothelial nitric oxide synthase (eNOS) expression and activity, and ultimately worsen capillary structural integrity. Moreover, it worsens diastolic dysfunction [74].

Plin5 also contributes significantly to the regulation of diabetic podocyte damage. Diabetic nephropathy is a serious complication of diabetes and is caused by hyperglucose-induced podocyte damage. By triggering Akt/GSK-3/NrF2-mediated apoptosis, oxidative stress, and inflammation, Plin 5 overexpression can reduce the damage excessive glucose causes to podocytes [72]. Plin5 overexpression leads to the enhancement of the Nrf2 pathway, which is related to GSK-3β regulation. Consequently, Plin5 controls oxidative stress and inflammatory injury through the Akt-GSK-3-Nrf2 pathway, reducing neuronal injury and podocyte injury brought on by oxygen-glucose deprivation/reoxygenation [72, 142]. In contrast, Plin5 silencing produced the opposite effect [72].

## Clinical intervention

### Monomer of Chinese traditional herbs

Sulforaphane, an electrophilic compound that is enriched in cruciferous vegetables such as broccoli, can reduce the expression of lipid droplet related proteins Plin2 and Plin5, reducing the number and size of lipid droplets both in vivo and in vitro [143, 144]. In addition, overexpression of PPARγ induces TAG accumulation and upregulation of Plin2 and Plin5, a process that cannot be reversed by sulforaphane [143]. These results suggest that PPARγ may be a target of sulforaphane in lipid metabolism. PPARγ may be a target of sulforaphane in regulating lipid metabolism in which Plin5 is involved.

Resveratrol, (3, 5, 4'-trihydroxystilbene) is a non-flavonoid polyphenol stilbene synthesized by plants [145]. In metabolically impaired individuals, resveratrol can increase IMCL content, especially Plin5-coated lipid droplets, leading them to develop a lipid droplet phenotype that mimics the "athlete like phenotype" [103]. In white adipose tissue, the effect of resveratrol in reducing lipid deposition was greater than strength training and cold therapy [146]. Therefore, it can play a better role in preventing lipid accumulation. ", promotes glucose homeostasis without affecting insulin sensitivity."

Glycycoumarin (GCM), an important coumarin compound isolated from licorice root, has good bioavailability. Both in vitro and in vivo experiments have confirmed that GCM can inhibit lipoapoptosis in nonalcoholic steatohepatitis mouse model by inhibiting endoplasmic reticulum (ER) stress, and the activation of Plin5-Sirt1 axis is involved in the protective effect of glycyrrhizin on hepatic lipotoxicity [147].

Curcumin ((1E, 6E) 21, 7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione), a major compound of turmeric, has been used in conventional medicine [148]. Together with PPAR and AMPK pathway activation, curcumin also boosted Plin5 gene expression in activated HSCS in vitro to promote the development of intracellular lipid droplets and sterol regulatory element binding protein and fatty acid synthase expression. In order to reestablish lipid droplet production and lipid accumulation in activated HSCS, adipocyte triglyceride lipase expression was downregulated [149].

### Antidiabetic

Dapagliflozin is one of sodium-glucose cotransporter-2 (SGLT2) inhibitors [150]. Studies have found that Dapagliflozin mediates the Plin5/PPARα signaling axis to significantly inhibit endothelin-induced abnormal cardiomyocyte hypertrophy and attenuate cardiac hypertrophy [151], which has a protective effect on the heart. Canagliflozin, the same type as dapagliflozin, was found to significantly alleviate the elevation of blood glucose and insulin resistance, inhibit the formation of atherosclerotic plaques and lipid accumulation in $ApoE^{-/-}$ mice. This conclusion was confirmed by the detection of ASS1, ASL, ARG1, MATLA, Plin5 and other markers [152]. This suggests that patients with diabetes and cardiovascular disease may be more likely to benefit from this class of drugs.

In addition, rosiglitazone, another type of hypoglycemic drug, does not change IMCL content when used in human body [153, 154], but the expression level and protein content of Plin5 and ADRP in skeletal muscle of T2DM patients are decreased [109], and insulin sensitivity is improved [109]. It is possible that the decrease of Plin5 and ADRP plays a role by promoting the decrease of recognized insulin desensitization intermediates such as diacylglycerol within lipid droplets [109]. Based on this speculation, their expression would be increased rather than decreased after insulin sensitizing intervention [155, 156]. Indeed, Phillips et al. [110] showed an increase in muscle ADRP protein and insulin sensitivity in obese nondiabetic subjects after weight loss interventions and in obese T2DM patients after pharmacologic interventions (metformin or troglitazone). This confirms that Plin5 and ADRP downregulation has potential therapeutic value for improving insulin sensitivity.

### Statins

Statins have been reported to reduce the hepatic expression of Plin5, which plays a key role in regulating hepatic fat accumulation and lipolysis. Uncertainty persists regarding Plin5's function and regulation mechanism in the statin therapy of nonalcoholic fatty liver disease. Recent studies have demonstrated that atorvastatin, which increases PKA-mediated phosphorylation of Plin5 and promotes lipolysis and decreases TG accumulation in the liver, decreased Plin5 expression in the liver without changing the protein level of Plin5 in the part of the liver lipid droplets in high-fat diet mice [157]. This brand-new method of atorvastatin reducing cholesterol could offer a fresh approach to the management of nonalcoholic fatty liver disease.

### Neuromodulator

Methobalamine, a neurotrophic drug used clinically, has also been shown to increase the expression of Plin5 derived from neural stem cells [28], promote intracellular liposolysis, reverse the imbalance of lipid metabolism and abnormal lipid droplet accumulation induced by excessive homocysteine, and further improve lipid homeostasis in regenerated bone.

Acetylcholine reduces palmitate-induced apoptosis of cardiomyocytes by promoting droplet lipolysis and Plin5-mediated lipid droplet mitochondria interaction [158], while inhibition of plin5 eliminates this effect. These findings may contribute to the development of new therapies targeting lipid-drop lipolysis and Plin5-mediated lipid-mitochondria interactions to prevent or alleviate lipotoxic cardiomyopathy.

### New materials

According to the property of lipid droplets to protect cells by sequesteling excess fatty acids, artificial lipid droplets, a new, safe and effective biomaterial to protect cells against oxidative stress and lipotoxicity, can significantly reduce the ROS induced by hydrogen peroxide and alleviate cellular lipotoxicity caused by excessive fatty acids [159]. This provides methods and potential therapeutic value for future research and medical applications of lipid droplets and their associated lipid droplet proteins.

## Conclusion

Insulin resistance, β-cell damage or apoptosis are important causes of T2DM, often accompanied by glucose and lipid metabolism disorders. Regulating glucose and lipid metabolism is an important measure for the prevention and treatment of T2DM. Many literatures have shown that Plin5 plays an important protective role in T2DM, such as improving insulin resistance of oxidized tissues such as heart, liver, skeletal muscle, promoting the browning of white adipose tissue, and protecting the function of pancreatic β-cells. Plin5 is located on the surface of lipid droplets, regulates the lipolysis process bidirectionally, and accelerates fatty acid utilization through lipid drops-mitochondria contacts, reducing the accumulation of free fatty acids in the cytoplasm and reducing lipotoxicity. Although it remains questionable whether Plin5 has a protective role in promoting cardiomyocyte compensatory cardiac hypertrophy, the regulatory mechanism in the athlete paradox remains to be further studied. Yet, it cannot be denied that Plin5 overexpression plays a critical part in enhancing lipid and glucose metabolism and safeguarding the injured target organs in T2DM. It also includes the possibility that useful treatments could involve regulation of the Plin5 biology that may not involve direct effects on Plin5 itself.

There are many similarities between the glucose and lipid metabolism disorders of T2DM and the hypermetabolism of cancer cells. As a bridge between T2DM and

cancer, Plin5 provides a new perspective for exploring the relationship between T2DM and cancer. At present, in addition to the application of hypoglycemic drugs and lipid-lowering drugs, the application of traditional Chinese medicine monomers, neuromodulatory drugs and new materials provides a new choice for the treatment of T2DM by targeting Plin5.

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M. W. and Y. W. wrote the main text. Y. Z. retrieve and organize the documents. Y. Q.had great contribution in second time revision, polishing manuscript. All the authors reviewed the manuscripts.

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**Data availability**
No datasets were generated or analysed during the current study.

## Declarations

**Ethics approval and consent to participate**
Not applicable.

**Consent for publication**
All authors agreed to publish the review.

**Competing interests**
The authors declare no competing interests.

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