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REVIEW ARTICLE

Roles of Perilipins in Diseases and Cancers

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Abstract: Perilipins, an ancient family of lipid droplet-associated proteins, are embedded in a phospholipid monolayer of intracellular lipid droplets. The core of lipid droplets is composed of neutral fat, which mainly includes triglyceride and cholesterol ester. Perilipins are closely related to the function of lipid droplets, and they mediate lipid metabolism and storage. Therefore, perilipins play an important role in the development of obesity, diabetes, cancer, hepatic diseases, atherosclerosis, and carcinoma, which are caused by abnormal lipid metabolism. Accumulation of lipid droplets is a common phenomenon in tumor cells. Available data on the pathophysiology of perilipins and the relationship of perilipins with endocrine metabolic diseases and cancers are summarized in this mini-review. The research progress on this family offers novel insights into the therapeutic strategies for these diseases.

Keywords: Perilipins, Lipid droplets, Lipid metabolism, Development, Diseases, Carcinoma.

1. INTRODUCTION

1.1. Lipid Droplets and Lipid Metabolism

Lipid Droplets (LDs) are dynamic organelles that store lipids and are surrounded by a phospholipid monolayer and several proteins found in almost all cell types. Triglycerides (TGs) in LDs are the largest energy reservoir in most organisms and are critical in regulating lipid and glucose metabolism [1]. Accordingly, saturating or exceeding the storage capacity of TGs lead to many different human diseases, including cardiovascular diseases, hepatic steatosis, diabetes, obesity, hyperlipidemia, and cancer [2]. Metabolic diseases arise from metabolic disorders associated with lipid, glucide, and protein. Recent discoveries on the biological characteristics and functions of LD have provided new insights into the mechanisms of these metabolic pathologies [3].

1.2. Perilipin Family of Lipid Droplet Associated Protein

Perilipins are major structural proteins located on the surface of LDs. LDs possibly play a crucial role in lipid homeostasis by mediating the transient storage of fatty acids in the form of triglycerides [4]. The early researchers discovered a protein that can be phosphorylated by protein kinase A on lipid droplet surfaces, and named this protein "perilipin" (PLIN1) [5]. Among perilipins, PLIN1 is the most widely studied, and the function of regulating adipocyte lipolysis has been well established [6]. With the discovery of PLIN1 in lipid droplet-associated proteins, the first three identified members were called the perilipin family. In 2010, Kimmel adopted perilipin as a unifying nomenclature for the mammalian perilipin-family (PLIN1-5) [7]. They are also involved in intracellular lipolysis or trafficking. The members of this family exist in various organisms, such as insects, fungi, slime molds, plants, and mammals [8]. Five members have been found in mammals: PLIN1 [9]; PLIN2 (adipocyte differentiation-related protein, or adipophilin) [10]; PLIN3 (47 kDa tail-interacting protein), also known as placental protein 17 (PP17) or mannose 6 phosphate binding protein 1 (M6PRBP1) [11]; PLIN4 (plasma membrane associated protein, S3-12, K1AA1881) [12]; and PLIN5 (myocardial lipid droplet proteins or MLDP, oxidative perilipins or OXPAT, lipid storage droplet protein 5, or LSDP5) [13] (Table **1**). In addition to PLIN4, the four other members have amino terminal sequence similarities and LD binding abilities. However, their tissue distributions, molecular sizes, affinities, and stabilities for binding to LDs differ [8]. Perilipin distribution is dependent on the utilization of tissues. They are divided into three categories according to their range of expression. The first category is composed of PLIN2 and PLIN3, which exist in various tissues and cell types [14]. The second category is composed of PLIN1 and PLIN4, which are restricted in adipocytes and steroidogenic cells [15].

1.2.1. PLIN1

PLIN1, a member of the first discovered protein family, is localized at the periphery of LDs and maintains the stabil-

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Table 1. Summary of the names of the five members.

Name Used Now	Other Names	Gene Location	Lipid Aggregation	References
PLIN1	Perilipin, Peri.	Human: 15q26; Mouse: 7 D3	Yes	[5, 6, 13, 16, 36]
PLIN2	Adipose differentiation-related protein, ADRP, Adipophilin, ADPH, ADFP	Human: 9p22.1; Mouse: 4 C4	Yes	[7, 11, 24, 25]
PLIN3	Tail-interacting protein of 47 kiloDaltons (TIP47), Placental protein 17 (PP17), Mannose 6 phosphate binding protein 1 (M6PRBP1)	Human: 19p13.3; Mouse: 17 D	Yes	[8, 12, 26]
PLIN4	S3-12, Plasma membrane associated protein, K1AA1881	Human: 19p13.3; Mouse: 17 D	Unknown	[9, 29, 30]
PLIN5	Oxidative PAT protein (OXPAT), Myocardial lipid droplet protein (MLDP), lipid storage droplet protein 5(LSDP5), PAT-1	Human: 19p13.3; Mouse: 17 D	Yes	[10, 14, 15, 31]

ity of LDs [16]. Interestingly, LDs are thought to be classic organelles that store energy in the form of TGs; structural proteins on the surface of LDs harmonize lipid homeostasis and participate in intracellular transport [17]. PLIN1 acts as a valve in lipid accumulation or depletion. Under non-phosphorylated status, TGs fail to undergo hydrolysis resulting in lipid deposition, whereas the phosphorylation of PLIN1 facilitates TAG lipolysis upon the stimulation of Adipose Triglyceride Lipase (ATL) and Hormone-Sensitive Lipase (HSL) during energy scarcity [18, 19]. Therefore, PLIN1 plays an important role in lipid metabolism. In addition, the mRNA of PLIN1 remains undetected in preadipocytes, but its mRNA expression increases remarkably during adipocyte differentiation. Compared with normal mice, PLIN1-null mice exhibit enhanced basal lipolysis and resistance to obesity induced by high-fat diet or heredity; the adipose mass of the model mice also decreases by approximately 70% [20]. PLIN1 serves as a protective coating against lipolysis [21].

1.2.2. PLIN2

PLIN2 is the first gene as associated with mRNA-induced preadipocyte differentiation at a level of RNA transcription, and PLIN2 protein has become a marker of adipocyte development [22]. PLIN2 protein is downregulated during the differentiation of preadipocytes to adipocytes and is undetected in mature adipocytes [10]. Under physiological conditions, PLIN2 protein is predominantly located and encased around the intracellular neonatal LDs. It disappears gradually during adipocyte differentiation and becomes replaced by PLIN1 protein; however, PLIN1 and PLIN2 mRNA can still be quantified at an mRNA level [23]. The conversion from PLIN2 to PLIN1 in preadipocytes implies that PLIN1 may perform additional functions that PLIN2 cannot provide. The stability of LDs is maintained by PLIN1, whereas the formation of LDs is promoted by PLIN2 [24]. PLIN2 is widely distributed in liver, skeletal muscles, macrophages, endotheliocytes, fibroblasts, adipocytes, and myoblasts [25, 26]. It is expressed in various malignant neoplasms, such as breast cancer, melanoma, multiple myeloma, and renal cell carcinoma [14]; thus, we suppose that this protein may be involved in the pathological mechanism of disease development. PLIN2 also participates in fatty acid uptake, LD formation, and lipid storage [27]. Moreover, PLIN2 is a marker of the accumulation of LDs under physiological and pathological conditions and of some diseases associated with metabolic dysregulation [28].

1.2.3. PLIN3

PLIN3 is a stable cytosolic protein when combined with LDs; furthermore, this protein is necessary in the transportation of intracellular mannose 6-phosphate receptors [11]. PLIN3 has a sequence structure analogous to PLIN1 and PLIN2; moreover, approximately 43% of sequence similarity exists in PLIN2 and PLIN3 [29]. The inhibition of PLIN3 prevents LD maturity and decreases the insertion of TGs into LDs. Under a relatively stable state, a dynamic change in proteins covered with budding LDs is observed; in PLIN2-null mice, PLIN3 may compensate for the absence of PLIN2 [30]. Unlike PLIN1, PLIN3 is expressed in almost all tissues, especially in macrophages, atherosclerotic plaques, and hepatocytes [7]. PLIN3 may play an important role in the onset of adipocyte differentiation, because this protein collects small LDs and participates in the budding of LDs [29, 31].

1.2.4. PLIN4

PLIN4 is identified as an adipocyte-specific protein during adipogenesis [12]. PLIN4 predominantly exists in White Adipose Tissues (WAT). At relatively low levels in the heart and skeletal muscles, PLIN4 is situated at the edge of skeletal muscle fibers. Thus, PLIN4 and PLIN3 are involved in the early stage of LD formation in adipose cells [32]. The expression of PLIN4 in skeletal muscles significantly decreases after a long-term exercise [33]. In PLIN4-deficient mice fed with high-fat-diet, cardiac steatosis is absent.

1.2.5. PLIN5

PLIN5, the newest members of the perilipin family, is involved in fatty acid catabolism and mitochondrial oxidation; it has also emerged as a putative key protein in lipid droplet function in oxidative tissues [34, 35]. PLIN5 is a

scaffolding protein that potentially regulates LD hydrolysis function in oxidative tissues; therefore, PLIN5 is highly expressed in skeletal muscles, liver, brown adipose tissues and adrenal tissues, particularly in the heart but not in WAT [36]. However, the role of PLIN5 in metabolic diseases remains controversial [37]. PLIN5 is constitutively localized in the mitochondria in skeletal muscle cells and cardiac myocytes [38]. Therefore, PLIN5 is related to the content of intramyocellular lipid. PLIN5 promotes the utilization and oxidation of fatty acids in skeletal muscle cells and cardiac myocytes [39]. Furthermore, the PLIN5 is located adjacent to PLIN4 and PLIN3, and the murine PLIN5 sequence is highly similar to PLIN2 and PLIN3 sequences [18]. Intriguingly, PLIN5 not only increases TAG accumulation, but also increases fatty acid oxidation paradoxically [40]. *PLIN2* and *PLIN5* genes exhibit similar transcriptional regulation in the absence of PLIN2. Thus, PLIN5 may play a compensatory role. Unlike PLIN1, PLIN5 is phosphorylated in a basal state, and phosphorylation remains unchanged with lipolysis under any stimulation [41].

Each member of perilipins generally shows tissue specific distribution and expression pattern. PLIN1 is specific to adipose tissues. PLIN2 and PLIN3 are the most abundant in almost all tissues. PLIN4 is expressed in WAT, although its role remains unknown. PLIN5 exists in oxidation tissues [42]. In this review, we integrated the function of these proteins, and provided a general outline of the differential expression of perilipins in intracellular lipid deposition, and endocrine metabolic diseases, and cancers, which lay a foundation for therapeutic strategies of these diseases.

2. REGULATION OF PERILIPINS

PLIN1 is a crucial regulator of lipid homeostasis. When energy is needed, PLIN1 promotes the hydrolysis of TGs under the catalysis of activating ATL and HSL. *PLIN1* is unequivocally regulated by nuclear hormone receptors of a peroxisome proliferator-activated receptor family member, namely, gamma (PPARγ), in adipocytes [43]. The mRNA expression of PLIN1 is increased through the regulation of thiazolidinedione, which is a PPARγ agonist, whereas antagonists yield opposite consequences. PPARγ binding to a PPAR-response element leads to the transcription of *PLIN1*, which has been detected in mice and humans [44]. Furthermore, PLIN1 is stimulated by PPARγ coactivator-1 alpha and inhibited by a small heterodimer partner; *PLIN1* is also a target gene of estrogen receptor-related receptor alpha, which is essential for energy balance, and PLIN1 is highly expressed during adipogenesis [45].

PPARγ (belongs to PPARs) that constitute one of the nuclear receptor superfamily. PPARs stand on the crosssection of multiple transcriptional signaling pathways and correlate well with various metabolic diseases and cancer [46]. PPARγ is a transcription factor that influences adipogenesis and glucose or lipid metabolism [47]. Simultaneously, PPARγ is overexpressed in fatty tissues and the expression of *PPARγ* gene is affected by promoting adipogenesis during preadipocyte differentiation, which is treated with mitogen activation protein kinase inhibitor and fibroblast growth factor-2 (FGF2) [48].

PLIN2 expression level increase through the regulation of three PPAR subtypes (alpha, gamma, and delta). PPARα is found in hepatocytes [49], PPARγ is located in trophoblasts [50], and PPARδ is detected in keratinocytes [51]. PLIN1 and PLIN2 are regulated by PPARs, whereas PLIN3 is different. The deletion of PLIN3 decreases the content of TGs instead of cholesterol, indicating that PLIN3 is involved in TG accumulation. PLIN4 is regulated by PPARs in a similar manner to PLIN1 and PLIN2 in adipocytes. PLIN5 is also influenced by PPARs through the activation of fatty acids, and PLIN4 is reduced in the liver and the myocardium in the absence of transcription factors [40]. It is also an essential gene for ATL to control lipolysis. The PLIN5 overexpression enhances the oxidation and catabolism of fatty acid. The deficiency of PLIN5 suppresses myocardial lipid accumulation and cardiomyopathy caused by type I diabetes because of PLIN5 that significantly inhibits lipolysis [52].

3. PERILIPINS AND DISEASES

3.1. Metabolic Diseases

Abnormal fatty acid metabolism leads to the accumulation of ectopic lipid, which causes metabolic disorders, such as obesity, insulin resistance, and liver steatosis.

3.1.1. Obesity

Obesity [53] is a metabolic disease caused by excessive calorie intake and reduced energy consumption, directly leading to an increase in adipocyte size and an excess of lipid storage and deposition. The morbidity rate of this disease has increased and has consequently threatened human health. Obesity is also associated with other metabolic diseases, and it frequently increases the risk of cardiovascular disease [54], hypertension [55], Diabetes Mellitus (DM) [56], and cancer [57]. The pathogenesis of obesity has been extensively investigated. Thus, treatments are necessary to prevent and control the increasing rate of this disease.

Morphologically, the number and size of fat cells are increased and accompanied by LDs in individuals with obesity [58]. The deficiency of PLIN1 is resistant to partial lipomatosis in humans compared with that in normal mice. PLIN1-null mice consume more food, but the former have normal weight and do not manifest diet-induced obesity [59]. *PLIN2* is reversible the leptin deficient (lepr) db/db obese mouse which in the absence of PLIN1 by increasing basal lipolysis [20]. In the presence of PLIN2, high-fat diet causes obesity in mice. Thus, PLIN2 deficiency can prevent obesity and fatty liver even with a high-fat diet [60].

3.1.2. Diabetes Mellitus

Diabetes Mellitus (DM) is a group of common metabolic diseases characterized by chronic hyperglycemia which is caused by a deficiency in insulin secretion or action. Approximately 80% of patients with DM die from cardiovascular complications [61]. The association between DM and excess intracellular lipid in non-adipose tissues has a notable significance relevance. The function of pancreatic islets is damaged upon prolonged exposure to lipids in mice fed with a high-fat-diet and in patients with diabetes [62].

PLIN2 protein is prominently expressed in pancreatic islet β cells of rats [63]. Insulin resistance is significantly

improved after the PLIN2 expression is inhibited by antisense nucleotides. Likewise, PLIN1 deficiency leads to diabetes in humans [64]. High glucose and insulin collaboratively increase the expression of PLIN3 in macrophages [65]. PLIN1 is used as a marker of adipocytes and is positively correlated with the amount of TGs in the pancreas. Rosiglitazone and thiazolidinediones are FDA-approved inhibitors of PPAR [66] and have been frequently used to treat diabetes and dyslipidemia [67]. Rosiglitazone improves insulin sensitivity in patients with obesity and T2D, but the PLIN2 expression increases in the former and decreases in the latter [68]. In human skeletal muscles, the expression levels of PLIN2 and PLIN5 proteins decrease after the PPAR agonist rosiglitazone is administered, but this treatment does not affect lipid metabolism; insulin sensitivity is also enhanced [69]. Furthermore, abnormal LDs accumulation is the major pathogenesis of diabetic cardiomyopathy. LDs are undetected in the hearts of PLIN5-knockout diabetic mice [70]. Therefore, the occurrence of diabetic cardiomyopathy has been improved in the model of PLIN5-knockout mice.

3.2. Cardiovascular Diseases

Atherosclerosis and hypertension are the most common age-related diseases that are main causes of death among the elderly.

3.2.1. Atherosclerosis

Atherosclerosis is the major pathological basis of cardiovascular diseases. Lipid accumulation and inflammation are vital for the formation of atherosclerosis [71], once lipids accumulate, macrophages become foam cells [72]. Foam cells are the characteristic pathological cells that appear in atherosclerotic plaques filled with LDs in the cytoplasm of macrophages [73]. PLIN1 is expressed in atherosclerotic plaques and macrophages. PLIN1-null mice showed exhibit an increased risk of atherosclerosis; therefore, PLIN1 helps prevent atherosclerosis [74]. Similarly, PLIN2 is detected in carotid endarterectomy plaques in humans [75].

PLIN2 is the main protein expressed in macrophages and foam cells in unstable atherosclerotic plaques. PLIN2 upregulation causes LD accumulation, its down-regulation prevents LD formation and remarkably reduces TG contents. After foam cells undergo apoptosis, their cytoplasm becomes released and forms atherosclerotic plaques, which eventually lead to thrombotic vessel occlusion [76]. In PLIN2 deficient mice, the ability of macrophages to convert to foam cells is reduced. Therefore，PLIN2 deficient mice are protected against atherosclerosis [77].

The range of atherosclerotic lesions decreases in PLIN2-deficient atherosclerotic mouse model; therefore, PLIN2-null mice are protected from atherosclerosis [77]. PLIN2 is specifically expressed in atherosclerotic plaques. This protein not only accelerates lipid accumulation but also limits intracellular cholesterol efflux [72, 78]. This protein also mediates the secretion of inflammatory cytokines, such as Tumor Necrosis Factor-α (TNF-α) and interleukin-6 (IL-6). Moreover, five different Single Nucleotide Polymorphisms (SNPs) have been noted in the human *PLIN2* gene, and these SNPs are associated with the localization of susceptible gene in atherosclerosis [79]. The reduction of PLIN2 can inhibit foam cells formation [80]. Therefore, the knockdown of PLIN2 gene may become an effective therapy of atherosclerosis.

The downregulated PLIN3 expression inhibits LD formation in macrophage foam cells and reduce TG contents. Therefore, PLIN3 may be a target gene for the prevention and treatment of atherosclerosis [81]. PPARδ can accelerate the accumulation of lipid in macrophages [82] and scavenge PPARδ in foam cells enhanced during inflammatory inhibition, which may diminish the region of atherosclerotic lesions for at least 50%. Accordingly, PPARδ may decrease inflammation and atherosclerosis [83]. Thus, the prevention of atherosclerosis by regulating these factors is the main purpose of this study.

PLIN5 is abundantly expressed in cardiomyocytes; under physiological conditions, PLIN5 inhibits lipolysis and controls lipid homeostasis in the heart [84]. Thus, aberrant triglyceride accumulation and cardiac steatosis are caused by an increase in the PLIN5 expression. Fatty acid oxidation decreases and lipid accumulation increases in the heart during myocardial ischemia. PLIN5 deficiency inhibits lipid accumulation in myocardial ischemia, and the TG content decreases in the heart [52]. PLIN5 deficiency plays a protective role in myocardial ischemia [85].

3.2.2. Hypertension

Hypertension is a chronic disease mainly caused by an increase in arterial blood pressure. Functional or organic changes in the heart, brain, kidney, and other important organs are triggered by hypertension. PLIN1 controls the balance between the storage and hydrolysis of TGs in adipocytes; anatomically, the adventitia of most systemic arteries is surrounded by a massive amount of perivascular adipose tissues (PVAT). In PLIN1-null mice, the amount of PVATs decreases as basal lipolysis increases [86]. Physiologically, PVATs secrete multiple vasodilatation factors [87]. Arterial remodeling and dysfunction play an important role in the occurrence of hypertension [88]. In addition, metabolic disorder and inflammatory cytokine overexpression lead to vascular sclerosis [89]. PVAT dysfunction in PLIN1-null mice induces vascular dysfunction and develops into spontaneous hypertension [90]. Adipose tissue abnormality in PLIN1-null mice can also cause hypertrophic cardiomyopathy [91].

3.3. Liver Disease

Ectopic fat accumulation in the liver leads to the formation of a fatty liver, which is characterized by LDs containing excessive neutral lipid in hepatocytes. The three general conditions of hepatic diseases are Hepatitis C Virus (HCV), Alcoholic Liver Disease (ALD), and nonalcoholic fatty liver disease (NAFLD) [92]. ALD and NAFLD are characterized by an extensive deposition of LDs in the cytoplasm of hepatocytes, and are manifested as a complication of obesity [93], and are also commonly associated with insulin resistance [94].

Most patients infected with HCV develop hepatic steatosis, cirrhosis, and hepatocellular carcinoma [95]. Perilipins are involved in the pathophysiology of hepatic steatosis, which is characterized by an inordinate accumulation of TAG in the hepatocytes [96]. PLIN1 is expressed in hepato-

cytes undergoing fatty degeneration. PLIN3 regulates the RNA replication of HCV, and the PLIN3 overexpression promotes the release of the virus. PLIN3 silencing reduces the release of infectious particles. PLIN3 terminates virus replication [97]. PLIN1 and PLIN2 are also overly expressed in human NAFLD. PLIN2-null mice are resistant to obesity induced by a high-fat diet and a fatty liver, and PLIN2 may protect the liver from lipotoxicity [98, 99]. Compared with a normal liver, a fatty liver with visible LDs stimulated by high fat diet exhibits an remarkably increased PLIN2 expression, and PLIN2 is positively correlated with lipidtartalom. PLIN2 deficiency attenuates hepatic steatosis and alters lipid metabolism [60]. ALD is a considerable health problem caused by alcohol abuse, and this condition leads to severe liver diseases. PLIN2 is essential for the formation of hepatic steatosis in mice chronically fed with alcohol, whereas its abrogation prevents the development of hepatic steatosis [99, 100]. In alcohol-fed mice, PLIN2 is overexpressed in human ALD and LDs observed prominently in ALD [101]. Conversely，the loss of PLIN2 possibly prevents hepatic lipid accumulation in the liver [102]. Therefore, PLIN2 plays an important role in ALD therapy [103].

In addition, the PLIN5 expression induced by an adrenergic receptor agonist increases in the liver of mice with severe hepatic steatosis. Therefore, an increase in the PLIN5 expression induces hepatic steatosis by inhibiting the release of fatty acids [104]. Perilipins are differentially expressed in hepatocyte steatogenesis and tumorigenesis *in situ* [105]. As previously mentioned, these proteins may be therapeutic targets. Therefore, a further understanding of their involvement in lipid metabolism will provide new insights into liver diseases and other related metabolic disorders.

3.4. Endocrine Disorders and Diseases

Polycystic ovary syndrome (PCOS) is a common endocrinopathy among women in their reproductive age, and its main etiological factors are menstruation cycle disorders, anovulatory sterility, and hyperandrogenism [106, 107]. PCOS may cause obesity [108], diabetes [109], atherosclerosis [110], hypertension [111], nonalcoholic fatty liver disease [112], and endometrial carcinoma [113]. Hyperliposis plays an important role in the formation of PCOS, and most women with PCOS have an abdominal and visceral fat distribution, which are irrelevant to the body mass index. Patients with PCOS have reduced lipolysis of adipocytes, indicating that adipose tissue dysfunction is implicated in the metabolic disturbances of PCOS, and exercise training increases the lipolysis of TAG [114]. A single nucleotide polymorphism of PLIN1 has been shown to exist in women with PCOS [115]. PLIN3 is highly expressed in adipocytes and preferably covers small LDs [29]; therefore, the PLIN3 expression markedly decreases in the adipose tissues of patients with PCOS because of high LD levels. Relevant research has shown that the protein and mRNA expression levels of PLIN3 increase after aerobic exercise training because the degree of adipose tissue lipolysis increases [116].

4. PERILIPINS AND TUMORS

In the early 20th century, Warburg [117] observed the difference between tumor cells and normal cells; they found that the former showed highly prefer glucose [118]. Under aerobic conditions, tumor cells convert glucose to lactic acid through the glycolytic pathway rather than utilize glucose through the mitochondrial oxidative phosphorylation, which is known as aerobic glycolysis or Warburg effect. Tumor cells are characterized by a more frequent proliferation and infiltration than those of normal cells. The rapid proliferation of tumor cell leads to an increase in energy requirement. Thus, their metabolism must be changed. Mounting evidences suggest that the lipogenic pathway is up-regulated in diverse human tumors [119].

4.1. Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the fifth most common cancer, and it is the third leading cause of cancer mortality [120]. Visible LDs exist in HCC. Scholars [121] studied the expression of perilipins in tumor and normal tissues through immunohistochemistry and optical microscopy, respectively, and they showed that the number of PLIN2-positive LDs in HCC cells is higher than that in normal hepatic cells. Abnormal lipometabolism occurs in various tumors and generates a series of changes in these molecules. Therefore, different kinds of pathological changes are observed. PLIN1, PLIN2, and PLIN3 are co-expressed in HCC [122]. In HCC carcinogenesis, the PLIN2 expression is related to cell proliferation, and it is upregulated during early tumorigenesis. However, the absence of PLIN1 is observed during the occurrence of HCC. This finding indicates that the lipogenic pathway is up-regulated in HCC, and it is a common mechanism in cancer [123]. These data indicated that the roles of perilipins in tumors associated with abnormal lipid accumulation should be further studied.

4.2. Sebaceous Carcinoma

Sebaceous Gland Carcinoma (SGC) is a rare cutaneous malignancy. Neoplastic lipogenesis is up-regulated in sebaceous carcinomas. Lipid accumulation is an important feature of sebocyte differentiation, and PLIN2 regulates the lipid accumulation of the sebaceous gland; in addition, PLIN2 is highly expressed in sebaceous glands, prominently in large vesicles and cytoplasmic vacuoles [124]. PLIN2-deficient mice show a significant reduction in the size of their sebaceous glands and have impaired sebaceous cells. PLIN2 is also increased during sebocyte differentiation. The specificity of PLIN2 immunostaining helps diagnose SGC. PLIN3 acts on sebocyte by regulating lipogenesis, and the loss of PLIN3 significantly disrupts neutral lipid accumulation [125]. Perilipins are differentially expressed in many kinds of tumors. LD accumulation is a common phenomenon in cancer cells [121], and the PLIN1 expression is limited to sebaceous adenoma and carcinoma. PLIN1 has been used as a marker of sebaceous epithelial and myoepithelial cells carcinomas of the parotid gland carcinomas [126].

4.3. Gastrointestinal Neoplasm

Gastric adenocarcinoma is a common gastrointestinal malignancy. Gastric adenoma and dysplasia are regarded as premalignant lesions of adenocarcinoma [127]. A White Opaque Substance (WOS) can be observed intuitively on the surface of gastric intraepithelial neoplasia through narrow-

band imaging endoscopy. WOS is more common in adenomas than in adenocarcinoma; therefore, WOS can be used to distinguish gastric adenoma from adenocarcinoma [128]. Furthermore, WOS contains LDs and deposits in the intestinal phenotype of patients with gastric neoplasia [129]. The distribution of LDs in gastric adenomas is different from that in adenocarcinomas. PLIN2 is a marker of lipid accumulation and detected in WOS-positive gastric epithelial neoplasia; these results are expected [130]. PLIN2 is expressed more frequently on the surface epithelium of low-grade adenomas than on the surface of invasive adenocarcinomas. PLIN2 may be a useful marker to distinguish between adenoma and adenocarcinoma [131]. Similarly, PLIN2 is expressed in well-differentiated colorectal adenocarcinoma but not in undifferentiated cases. Therefore, the PLIN2 expression is closely related to the intestinal differentiation of gastric adenoma and adenocarcinoma. PLIN2 is a useful marker for the diagnosis of colorectal cancer initial stages [132].

4.4. Lung Adenocarcinoma

Lung cancer is common malignant tumor, and its incidence has increased. It is often diagnosed in the terminal stage and is associated with a low survival rate. Adenocarcinoma is the most common pathological type of lung cancer [133]. However, the prognosis of lung cancer has yet to be fully understood. Studies show PLIN2 is involved in carcinogenesis [28]. The PLIN2 expression is increased in pulmonary adenocarcinoma and squamous cell carcinoma compared with its expression in normal tissues. Therefore, PLIN2 plays an important role in the tumorigenesis of pulmonary adenocarcinoma, and PLIN2 is a marker for the diagnosis of lung adenocarcinoma [134]. However, the expression of PLIN2 is not related to clinical-pathological factors. The molecular mechanism of lung adenocarcinoma should be further examined.

4.5. Cervical Carcinoma

Cervical cancer caused by human papilloma virus is one of the most common malignant tumors in females. It has been reported that PLIN3 is overexpressed in squamous cervical carcinoma tissues compared with normal cervical epithelium (negative for PLIN3) [135] and HeLa (squamous cervical cancer) cells [136]. In the case of metastases or pregnancy, the expression of PLIN3 in squamous cervical carcinoma tissues and normal cervical epithelium is the same. The serum PLIN3 level is elevated in patients with invasive carcinoma, and is declined after treatment and is elevated again in relapse [137]. Thus, PLIN3 is a possible biomarker for cervical cancer [138].

Perilipins may be used as therapeutic targets, and they are associated with the dysregulation of lipid and carbohydrate metabolism [139]. Gene knockout experiments have shown that the function of intercellular LDs is impaired, thereby preventing the accumulation of LDs [90]. The inhibition of perilipins can prevent cell proliferation, induce tumor cell apoptosis *in vitro*, and inhibit xenograft tumor growth [20, 59, 122]. Currently, only a few studies on tumors have been reported, and more research studies are needed in the future.

CONCLUSION

Taken together, the accumulation of ectopic fat is associated with metabolic diseases, but the molecular mechanisms of these diseases are poorly described. PLIN1-5 play important roles in lipid metabolism and carcinogenesis. Perilipins are closely linked with endocrine metabolism diseases and cancers (Fig. **1**). The accumulation of LDs is a common phenomenon in tumor cells. In addition, perilipins are differentially expressed in tumors, and proteins or PPARs may influence the metabolism of tumor cells. Perilipins may also resist cancer. Perilipins are involved in metabolic diseases and cancers, but further investigations and clinical trials are necessary to elucidate the mecha-

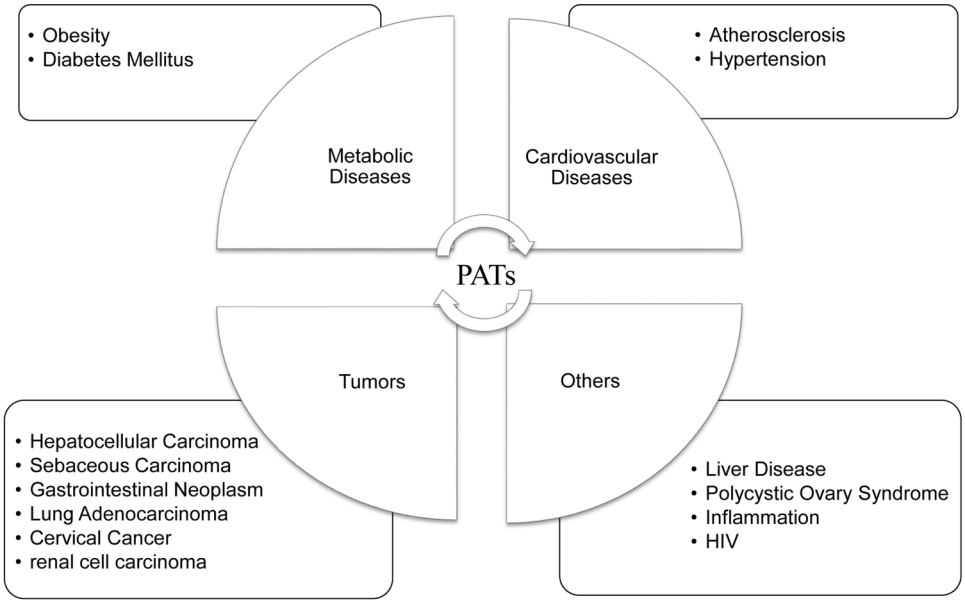

Fig. (1). Perilipins are closely linked with disease and cancers.

nism of perilipins in metabolic diseases and cancers. Therefore, favorable perspectives on potential therapeutic approaches for malignancies should be developed. Further studies should also be performed to enhance the understanding of the direct roles of perilipins in the pathogenesis of age-related diseases, such as endocrine metabolism diseases. The inhibition of perilipins can prevent cell proliferation, cause tumor cells apoptosis *in vitro*, and inhibit xenograft tumor growth. Blocking perilipins likely provides novel opportunities for the prevention and treatment of lipid accumulation-related diseases.

LIST OF ABBREVIATIONS

ALD	=	Alcoholic Liver Disease
ATL	=	Adipose Triglyceride Lipase
DM	=	Diabetes Mellitus
HCC	=	Hepatocellular Carcinoma
HCV	=	Hepatitis C Virus
HSL	=	Hormone-Sensitive Lipase
IL-6	=	Interleukin-6
LDs	=	Lipid Droplets
NAFLD	=	Non-Alcoholic Fatty Liver Disease
PCOS	=	Polycystic Ovary Syndrome
PPARγ	=	Peroxisome Proliferator-Activated Receptor gamma
PVAT	=	Perivascular Adipose Tissue
SGC	=	Sebaceous Gland Carcinoma
SNPs	=	Single Nucleotide Polymorphisms
TGs	=	Triglycerides
TNF-α	=	Tumor Necrosis Factor-α
WAT	=	White Adipose Tissue
WOS	=	White Opaque Substance

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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