Future Journal of Pharmaceutical Sciences

REVIEW

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Lipid droplets associated perilipins protein insights into finding a therapeutic target approach to cure non-alcoholic fatty liver disease (NAFLD)

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Abstract

Background: Non-alcoholic fatty liver disease (NAFLD) is now the most common form of chronic liver disease in the world, and it's linked to a slew of other risk factors including diabetes, obesity, dysbiosis and inflammatory bowel disease. More than 30 years ago, a patient was diagnosed with fatty liver with excessive fat accumulation in hepatocytes, a disorder known as hepatosteatosis. There will be no promising therapeutic medicines available from 1980 to 2021 which can reverse the fatty liver to normal liver state. In this review, we highlighted on lipid droplet associated protein which play a major role in accumulation of fat in liver cells and how these cellular pathway could be a promising therapeutic approach to treat the fatty liver disease.

Main body: Over the last few decades, Western countries follow a high-fat diet and change their lifestyle pattern due to certain metabolic disorders prevalence rate is very high all over the world. NAFLD is a major health issue and burden globally nowadays. Researchers are trying to find out the potential therapeutic target to combat the disease. The exact pathophysiology of the disease is still unclear. In the present decades. There is no Food and Drug Administration approved drugs are available to reverse the chronic condition of the disease. Based on literature survey, lipid droplets and their associated protein like perilipins play an eminent role in body fat regulation. In this review, we explain all types of perilipins such as perilipin1-5 (PLIN1-5) and their role in the pathogenesis of fatty liver which will be helpful to find the novel pharmacological target to treat the fatty liver.

Conclusion: In this review, majorly focussed on how fat is get deposited into hepatocytes follow the cellular signalling involved during lipid droplet biogenesis and leads to NAFLD. However, up to date still there mechanism of action is unclear. In this review, we hypothesized that lipid droplets associated proteins like perilipins could be better pharmacological target to reverse the chronic stage of fatty liver disease and how these lipid droplets associated proteins hide a clue to maintain the normal lipid homeostasis in the human body.

Keywords: NAFLD, Perilipin, Lipid droplets, Lipolysis, Hepatosteatosis

Background

NAFLD is proportionately increasing worldwide if we look globally it has been estimated that one-fourth of the total population is affected by the NAFLD up to 2010 [1, 2]. Epidemiological data suggest that the prevalence rate of metabolic diseases increases concomitantly in present time. A meta-analysis study by Younossi et al. [3]

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reported the rate of prevalence in US community about 24%. NAFLD is characterized by excessive fat accumulation in hepatocytes but to define this disease the fat is accumulated in the hepatic system which covers more than 5% area in the histologic biopsy of the liver is known as a state of non-alcoholic fatty liver or simple steatosis [4, 5]. Histopathological studies revealed that after fat accumulation in hepatocytes it shows hepatocytes ballooning, steatosis, inflammatory damage of hepatocytes, Mallory's hyaline, hepatocellular hyper-atrophy and fibrosis from Non-alcoholic fatty liver stage to liver cirrhosis stage [6–8]. In the case of children, Mallory's hyaline is absent in NAFLD state [9]. These all histopathological features are a major hallmark for the NAFLD, and its further progression leads to the non-alcoholic steatohepatitis (NASH) and continued progress in disease characterization further leading to cirrhosis condition or causes liver cancer. The NAFLD progressed to chronic fatty liver disease by certain risk factors such as obesity, type 2 diabetes mellitus, insulin resistance, hyperlipidemia, environmental factors, genetic factors and lifestyle changes after that increase the mortality rate worldwide [10–14]. Among those factor obesity is more prone for fatty liver diseases which is mainly cause's steatosis condition which a hallmark for fatty liver diseases [15–18]. Obesity factor and fatty liver diseases happened due to highly fat accumulation in liver hepatocytes and triglycerides level which is mainly caused by dysfunction in fat uptakes mechanism and lipid biogenesis. Apart from disease risk factors and lifestyle pattern, lipid droplets and their biogenesis play an impactful role in fat accumulation in a different part of the body which involve in lipid synthesis and fat metabolism [19].

In this scenario, LDs are highly involved to maintain the lipid homeostasis. Several LDs associated protein can be proved as a potential target for metabolic diseases and fat related disorders. Different types of Perilipins PAT domain (perilipin, Adipophillin and tail interacting protein 47) proteins are crucially involved in disease pathogenesis which leads to highly fat accumulation. Based on disease severity, we have to find out the potential therapeutic target to visor less the disease pathway.

Main text

Worldwide around one-fourth of the total population are affected by NAFLD a disease which indicates major health problems [2, 3]. Mostly these cases further progression leads to chronic liver diseases such as liver cirrhosis condition which ultimately leads to mortality factor in fatty liver patients. Disease progression to severe case of fatty liver condition caused by certain risk factor such as diabetes, obesity, insulin resistance dyslipidaemia, inflammatory and certain metabolic disorders [20, 21]. Apart from that several key regulator of fatty acid synthesis and their metabolism upon disruption leads to disease state. Based on clinical shreds of evidences, lipid droplets are one of them which highly participate in the fat regulation.

Generally, LDs are the dynamic organelle covered by a monolayer of phospholipid membrane, and these droplets are stored neutral lipids such as triacylglycerol, stearic acid, sterol ester which is helpful in cell membrane synthesis, cell signalling and hormonal synthesis and maintain normal lipid homeostasis [22–24]. However, increase the synthesis and secretion of LDs from ER membrane and transfer to cytosol increase the neutral lipid deposition and fatty acid intracellularly which causes several physiological impairments such as steatosis, inflammation, ER stress, insulin resistance, mitochondrial dysfunction, generation of free radicals and reactive oxygen species (ROS) due to cellular toxicity happened[25]. Impairment in the normal physiological function of lipid droplets interferes with several types of function which causes metabolic disorders such as cardiac complications, fatty liver, obesity, inflammation and cancer-like disorders [26–28]. Alternatively, all these factors involved in metabolic disorder [25].

Reported data suggest that there is not any Food and Drug Administration (FDA) approved drug that is available in the market for treatment of fatty liver disease or to reverse the liver fibrosis condition. According to research findings we targeting the disease from more than 30 years but due to the severity of the disease, we cannot beat the fatty liver till now. Based on supportive data, LDs formation and proteins involved in the storage of neutral lipids may be proven as a potential target to combat fatty liver and associated metabolic disorder. At present time, also the role of LDs and their exact cellular pathway are unclear to understand the metabolic associated disorder.

LDs play a key role in lipid homeostasis, and lipid droplets are considered the major site for storage of neutral lipids, and it provides the energy to cells in fasting state and also help in lipid synthesis and membrane synthesis lipid droplets are understand complex and dynamic organelles which play a central role in lipid regulation [29]. LDs have a distinct and complex structure which have hydrophobic central core which is surrounded by a monolayer which consists of several lipids and family of various proteins [30].

LDs formation and there biogenesis process depend upon various endoplasmic reticulum enzymes and protein for normal lipid homeostasis these enzymes Di-acyl glycerol's acyl transferase (DGAT), lipin, Glycerol-3-phosphate acyltransferase (GPAT), etc., and various proteins most abundantly perilipin family protein, Cell death inducing DFF45-like effector (CIDE) family of

proteins and fat inducing transmembrane protein (FITM) dysfunction are highly involved in LDs accumulation in case of NAFLD [31]. On the behalf of reported data, this lipid droplet associated proteins and endoplasmic reticulum-associated enzymes can be a potential target for NAFLD in a future perspective [31, 32].

So in this article, we focussed on certain checkpoints of LDs formation and what is the exact role of these LDs associated perilipin proteins in fatty liver disease progression.

Lipid droplet formation

Based on recently supportive data, the formation of LDs is unsolved mystery till now researcher are trying to understand the exact signalling and their mechanism involve in lipid homeostasis and in metabolic associated disorders.

LDs consist of various types of neutral lipids in the hydrophobic central core such as triglycerides, steryl-esters, retinyl-esters, etc., which is covered by a monolayer of phospholipids and various decorated proteins of different families [30, 33–35]. These stored neutral lipids are helpful in membrane synthesis, steroidal hormone synthesis and energy reservoir for intracellular processes [36]. However, some study shows that lipid droplets formation happened by de novo process, and it can be possible that mature and large size LDs formation occur from existed LDs with the help of LDs-LDs fusion process because several proteins are present on the lipid droplet surface which participate infusion process such as fat specific protein 27 (FSP27) which is highly expressed in the case of large size LD formation [37, 38]. FSP27 protein is the member of CIDE family protein also known as cell death inducing DFF45-like effector C (CIDEC) which is highly expressed in NAFLD state which is associated with enlargement of lipid droplets [39–41]. Another best-proposed model according to a recent study indicates that the formation of LDs involved three steps in the smooth endoplasmic reticulum. Firstly neutral lipids are synthesized and then by some membrane-bound O-acyltransferase enzymes in endoplasmic reticulum (ER) that these neutral lipids are then accumulated in the bilayer leaflets of the endoplasmic reticulum and create a lens like formation because excess neutral lipids decrease the tension of bilayer [42] and increase the surface tension of lipid droplets that can be bud from endoplasmic leaflet bilayer, and it is also mentioned clearly that triglycerides also synthesized by DGAT1 and DGAT2 from diacylglycerol [43] and monoacylglycerol in bilayer membrane of ER during lipid droplet formation after budding, the phospholipid monolayer consisting of vesicles are detached from the ER, and formation of LDs happened shown in Fig. 1 [36, 37, 44].

A mature lipid droplet covering consist of a monolayer of phospholipids which is decorated by several families of proteins and lipids which play a key role in fatty liver disease or accumulation of fats in hepatocytes. In the future, these may be can be proved as a potential target for combat fatty liver disease. In this review article, we will be focussed on how lipid droplet-associated proteins are

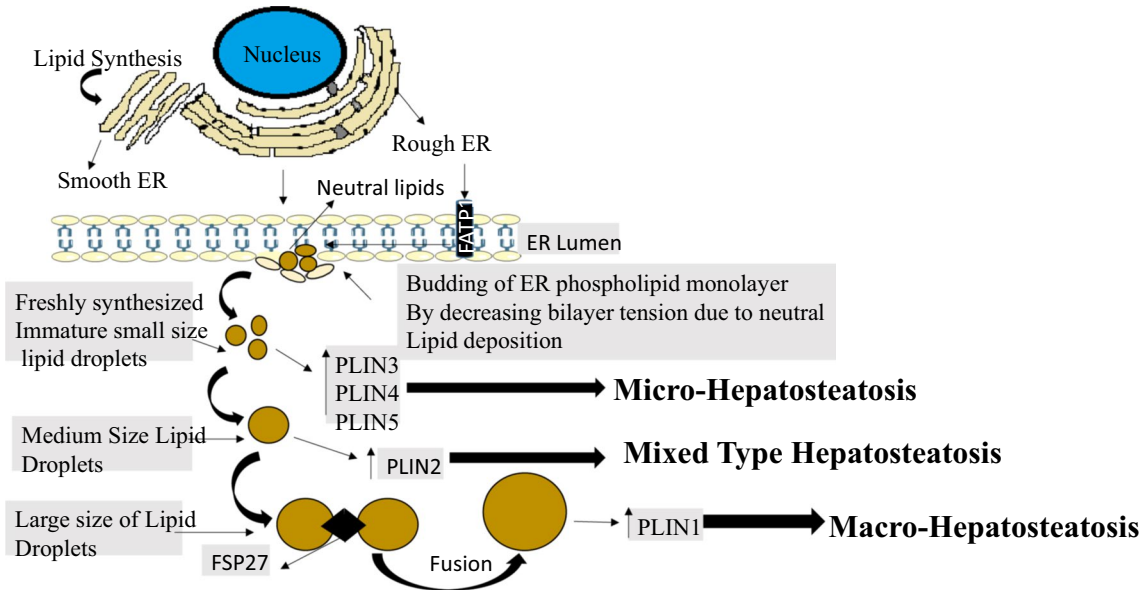

Fig. 1 Represents synthesis of lipid droplets from smooth endoplasmic reticulum with their associated proteins. *ER* endoplasmic reticulum, *FATP1* fatty acid transporter protein 1, *FSP27* fatty specific protein 27, *PLIN* perilipin

involved in metabolic disorders. We majorly focus in this review on perilipins which further subdivided and how it is main player in LDs formation and involved in the metabolic disorder. However, emerging research report claimed that in future it can be a potential target to combating the metabolic disorder [19, 45].

Functional role of perilipins

Lipid droplets monolayer are decorated with various types of proteins, perilipins family of proteins is one of category all of them which is majorly involved in hepatosteatotic condition. Perilipins are further categorized into five type after their nomenclature which named as PLIN1, PLIN2, PLIN3, PLIN4, PLIN5 [46, 47]. Lipid droplets exist all over the body which serve a major function in lipid homeostasis but the perilipin play a different physiological role. Clinical findings claimed that PLIN2, PLIN3, PLIN5 are majorly express in the heart, liver and skeletal muscle but PLIN2 mostly expressed by non-adipose tissue. Somewhere reported that PLIN5 abundantly observed in oxidative tissue like heart, skeletal muscle and liver as per shown in Fig. 2 [48, 49]. The functional role of different perilipins are shown in the Table 1

Perilipin 1 (PLIN1)

Perilipin1 protein mostly expressed by mature adipocytes, and it is majorly expressed in large size of lipid droplets which causes the macrovesicular steatotic conditions in our hepatocytes [50]. PLIN1 overexpression causes hepatocellular ballooning because it interacts with fat specific protein 27 which is a CIDEC protein and help in fusion between two lipid droplets and make a large mature lipid droplets which store the neutral lipids. Perilipin1 is present on the surface of lipid droplets, and its phosphorylation is regulated by the cAMP dependent protein kinase A (PKA) [50, 51].

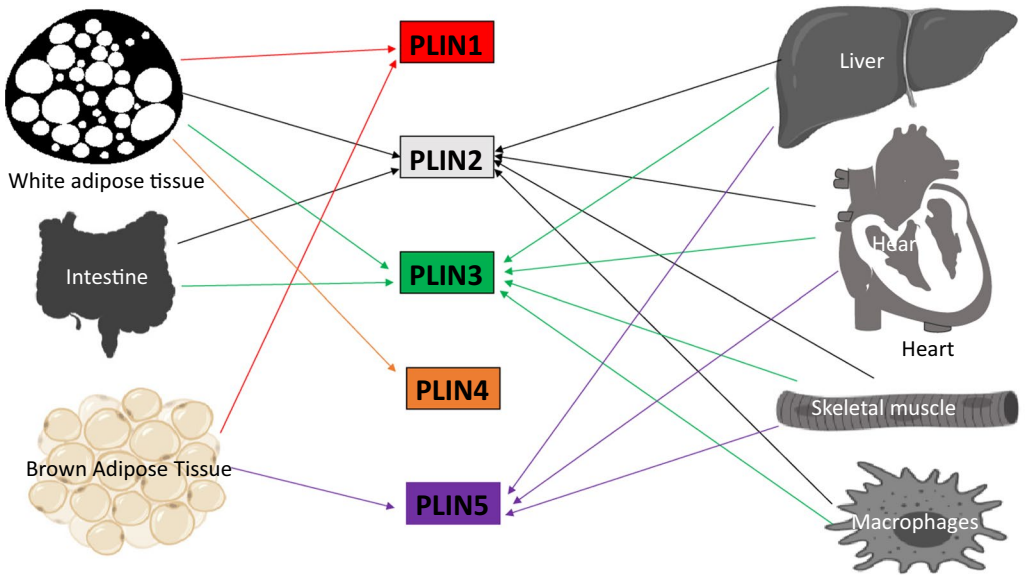

Fig. 2 Represents distributions of different perilipins in different part of body

Table 1 Represents functional role of perilipins

S. no.	Name of perilipins	Functional role
1	Perilipin 1	Lipid droplet size enlargement, deposition of neutral lipid, causes excessive fat deposition with Macro Hepatosteatosis condition, phosphorylation of PLIN 1 leads higher rate of lipolysis
2	Perilipin 2	Express in mixed type hepatosteatosis, higher PLIN 2 expression leads SREBP activation, activation of lipid synthesis, maturation of lipid droplets from nascent
3	Perilipin 3	Move cytosolic to nascent lipid droplets from ER lumen, Increase expression of Hepatitis C virus core protein, associated with inflammatory pathways like PGE2, COX-2, etc.
4	Perilipin 4	PLIN-4 expressed like PLIN-3 in nascent lipid droplets, leads micro hepatosteatosis condition
5	Perilipin 5	Micro Hepatosteatosis, over expression recruits mitochondria and increase beta oxidation, prevent direct cellular lipotoxicity

PLIN1 majorly participate in lipolysis, reported data suggest that catecholamines are the primary source for initiation of lipolysis through beta adrenergic receptors which activate the protein kinase A in phosphorylated manner, so this signalling cascade also phosphorylate the PLIN1 which recruit the hepatic sensitive lipases and other enzymatic proteins which initiate the lipolysis shown in Fig. 3 and 4 [52, 53]. Recent study shows that perilipin knock out mouse protect against fat deposition and also shows that leanness with more food consumes as compare to control and body weight also remained same [54]. Hepatic sensitive lipase (HSL) plays a key role in lipolysis process which hydrolyse the triacylglycerol into free fatty acid this action inhibited by the perilipin which cover the lipid droplets and increase the lipid droplet size with adipose tissue mass [52, 53]. Hence,

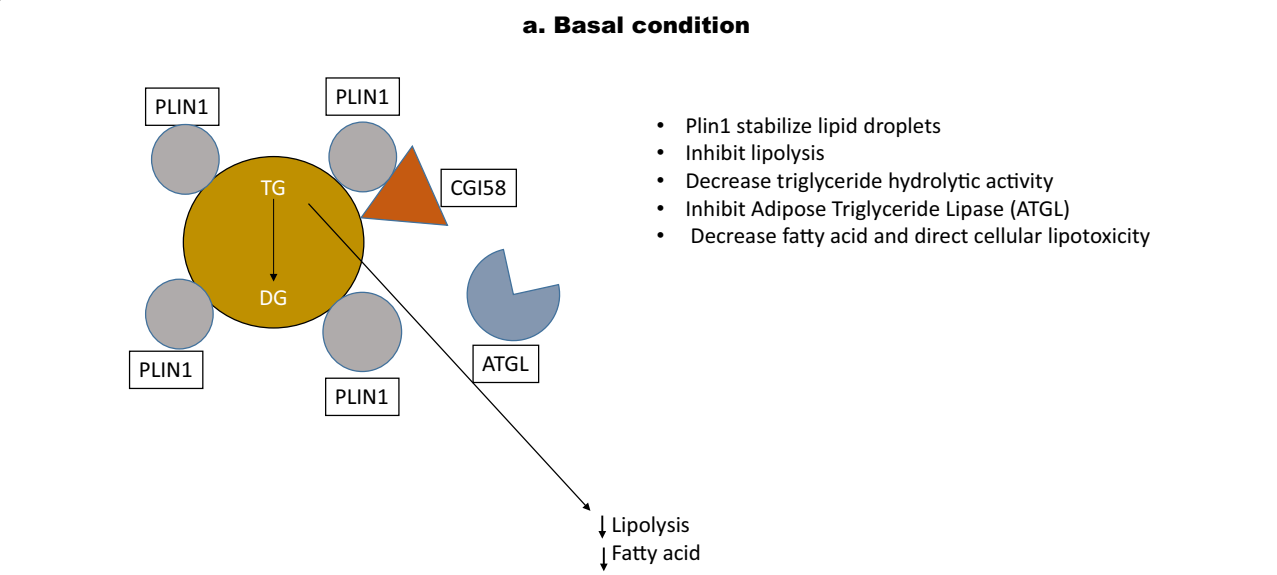

Fig. 3 Represents the decreasing level of lipolysis and fatty acid at basal condition ruling by perilipin and other lipid droplet associated protein

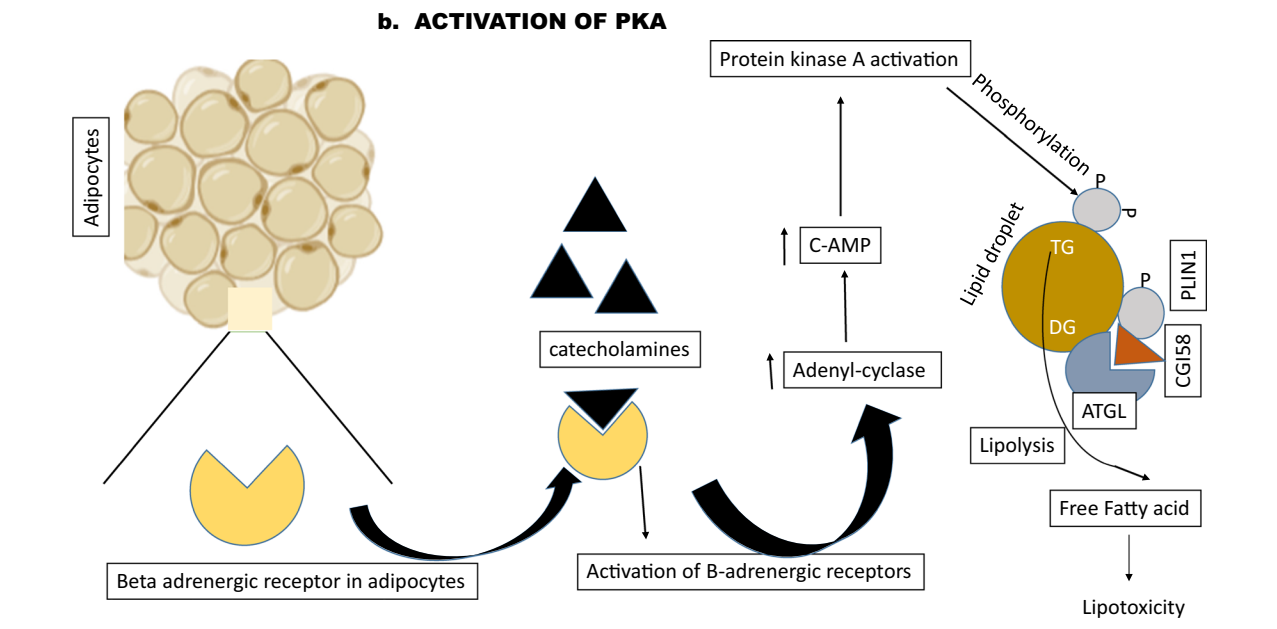

Fig. 4 Represents the activation of PKA leading to phosphorylation of perilipins and activate the ATGL to cause lipotoxicity

this perilipins maintains normally lipid homeostasis and other body function which is unknown at that time but it can be potential target for obesity related disorder.

PLIN1 is closely associated with obesity induces insulin resistance condition which has been proved after study on plin1 knock out mice observed very lean and somewhere, the lipolysis rate also increased. One study claimed that release of cytokines in metabolic diseases such as Tumor Necrosis Factor (TNF-α) decrease the transcription level of PLIN1 and concomitantly increase level of basal lipolysis [28]. After TNF-α administarations in human and in rodents, clinical data give surprisingly more fatty acid exposure intracellularly and in systemic circulation also impove insulin resisstance condition in patient of obesity but TNF-α null mice shows reduction in insulin resistance and also shows lower amount of free fatty acid detected in plasma [55]. However, in obese patient the number of lipid droplets and there accumulation is increases in adipocyte, so TNF-α stimulation increase the adipocytes lipolysis at basal level [56, 57]. Researcher has been proposed that TNF-α also follow cAMP/PKA pathway and which causes phosphorylation of perilipins and increase the lipolysis at basal level [55].

Role of perilipin 1 and CIDEC

CIDEC or FSP27 has an eminent role in lipid droplet biogenesis and abundantly expressed in white adipose tissue and brown adipose tissue. Studies claimed that during adipogenesis the expression of fat specific protein 27 increases gradually. It has been proved that in preadipocytes cells increase the content of neutral lipid and their storage with overexpression of FSP27 and enlargement in size of lipid droplets has been observed. In one study, after Oil Red O staining of transfected FSP27 cells shows higher intensity when compared with non-transfected cells which proved that the FSP27 transfected cells have higher neutral lipid contents [58]. Mainly this protein is highly responsible for lipid droplet enlargement [59]. It is possible by LD's-LD's fusion process. Fat specific protein 27 is involved in fusion process that it form the clustering and fused one lipid droplets to another make a large size of LDs and also increase the accumulation of triacylglycerol's and their storage [60].

Perilipin 2 (PLIN2)

PLIN2 is also named as adipose differentiation related protein (ADRP) because it is highly overexpressed in adipose tissue during adipocyte differentiation bioprocess and PLIN2 expression also depend on the lipid droplet size that it is proved that medium size of premature lipid droplets associated with higher expression of PLIN2 but after maturation of lipid droplets PLIN2 is replaced by the PLIN1, and medium size LDs convert into large one and causes the macrovesicular hepatosteatotic condition [50].

Perilipin family proteins are attached to the surface of lipid droplets in which PLIN2 majorly found in cytosolic lipid droplets surface, and reported data suggest that PLIN2 is overexpressed in NAFLD and causes hepatosteatotic condition [61, 62]. Recent studies indicate that knockout PLIN2 (ADRP) mice are shows improvement in NAFLD or steatotic condition, and it is hypothesized that Sterol regulatory elementary binding protein (SREBP) activation is highly involved in de novo lipogenesis, however, PLIN2 knockout mouse supress or impair the SREBP signalling which involved in the de novo lipogenesis and causes the fatty liver [50, 63]. Another study claimed that if perilipin 2 downregulate via treatment with antisense oligonucleotide in vivo, significantly reduction observed in triglycerides level of leptin obese mice [64].

PLIN2 or adipose differentiation related protein mostly associated with the lipidation and maturation of lipid droplets with the help of Cell death inducing DFF45-like effector-B (CIDEB) protein that it is believed that overexpression of PLIN2 prevent the lipolysis of lipid droplets and increase the activation of lipid synthesis however, on the behalf of reported data perilipin 2 overexpression inhibit the activity of ATGL which help in lipolysis of triglycerides which hydrolyses the triglycerides into free fatty acids [65]. PLIN2 also correlate with very low density lipoproteins (VLDL) that it is proved that cytosolic lipid droplets directly transfer the triacylglycerol to pre-VLDL particles in ER lumen and also internally ER lipid droplets also transfer their triacylglycerol into mature VLDL by fusion process, so here PLIN2 which is a LDs surface protein plays a major role in formation of VLDL assembly and maturation via CIDEB which is present in Golgi-apparatus.

Nascent VLDL particles are synthesized into ER membrane, and these are packed into special biological vesicles which is transport from ER membrane to Golgi apparatus where these VLDL particles are attached to ApoB-100, and some post translational modification happened such as glycosylation and phosphorylation then attach CIDEB to ApoB-100 and VLDL particles are matured and then budding from the ER membrane and transfer to the cytosolic part. However, CIDEB has a prominent role in maturation and in lipidation process [66, 67]. Preclinical studies in CIDEB null mice show increase expression of PLIN2 but surprisingly knock down of PLIN2 in CIDEB null mice shows good reduction in triacylglycerol's level [65].

Perilipin 3 (PLIN3)

Initially PLIN3 characterized as a mannose-6 phosphate binding proteins but after found their role in lipid droplets which is proved as a lipid droplet surface protein then functionally categorized under perilipin family, and it is also known as tail interacting protein (47 kDa), after reviling the data of proteomics and association with LDs and share the sequence homology with PAT domain help to renamed as a PLIN3 protein [68]. Furthermore, TIP47 protein shares sequence homology matched with two lipid droplet associated proteins named as perilipins and adipocyte differentiation-related protein (ADRP) which play an effective role in lipid droplet biogenesis or localization [69, 70]. TIP47 localized from cytosolic to nascent lipid droplets that this evidence claimed after HeLa cells culture medium were treated with fatty acids for increment in neutral lipids such as triacylglycerol's and retinol. After increasing level of triacylglycerol's surprisingly decrease in cytosolic TIP47 was observed and increasing pattern of TIP47 protein measured in nascent lipid droplets which shows further confirmation for TIP47 which is associated with nascent lipid droplets [70].

It has been proposed that lipid droplets are also found in all types of inflammatory cells and specially proved that number and size of lipid droplets were increased in the macrophages and eosinophils during inflammation conditions [71]. Recent finding has been proposed that there is some association of PLIN3 with Prostaglandin E2 (PGE2) production during inflammation, for proved that HL-60 derived neutrophils are treated with lipopolysaccharides, PLIN3 was showed overexpression with PGE2 production. But cells were treated with siRNA for downregulation of PLIN3, it also showed decrease production of prostaglandins synthase and cyclooxygenase-2 which synthesize the PGE2. Hence that reduction of PLIN3 also shows that reduction PGE2 production and may be play an essential role in fatty liver disease with less cellular damage by inflammation [68].

However, TIP47 majorly involved the trafficking of lysosomal enzymes and mannose-6-phosphate receptors from endosomes to trans-Golgi networks but knockdown studies of TIP47 show surprisingly there is no effect on mannose-6-phosphate receptors localization from endosomes to trans-Golgi networks but it disturb the maturation of lipid droplets and also impaired the introduction of triacylglycerol's into lipid droplets which provide a strong evidence PLIN3 play a key role in lipid droplet biogenesis [46, 72]. Furthermore, PLIN3 may be good target in steatotic condition.

Recently published data showed that Hepatitis C virus (HCV) infected patient shows massive hepatic steatotic condition due to overexpression of HCV core protein. Somewhere, PLIN3 associated with initiation of HCV core inducing steatotic condition. Based on supported data PLIN3 knockdown study indicates that improvement in steatotic condition of hepatocytes [73].

Perilipin 4 (PLIN4)

Perilipin 4 has unique function among the all perilipins proteins that it is abundantly found in the white adipose tissue and absent in liver and other oxidative tissue like heart and skeletal muscle [74]. PLIN4 doesn't share their sequence homology in PAT domain, like other perilipins except Perilipin 1, and only this perilipin consist the 11 mer-repeat motifs which make a distinct impact from all other perilipins [50, 51, 74]. PLIN4 is also termed as S3-S12 due to their repeat motifs, and it has been proposed that PLIN4 expression was observed in nascent lipid droplets in cytosolic part [48, 51, 75]. Perilipin4 expression in nascent lipid droplets confirmed that it is incorporated newly synthesized triacylglycerol's into nascent lipid droplets, and upregulation of PLIN4 shows the micro-steatotic condition in hepatocytes [50].

It can be possible that there is a connection between PLIN4 and PLIN 5 expression because PLIN4 abundantly present in white adipose tissue and absent in oxidative tissue like heart, liver and skeletal muscle wherever PLIN5 is almost absent in white adipose tissue and highly expressed by oxidative tissues. Reported data claimed that somewhere inactivation of PLIN4 downregulates the PLIN5 expression and also reduced the triacylglycerol's level in cardiac cells without affecting any other perilipins [74].

Perilipin 5 (PLIN 5)

Like all other perilipins, PLIN5 is also lipid droplet surface protein which is highly expressed in non-adipose oxidative tissue like heart, liver and skeletal muscle tissue [49]. PLIN5 plays a complex role in lipid homeostasis. Emerging data suggest that there is a crosstalk happen between mitochondria and PLIN5, and recently researcher claimed that PLIN5 overexpression on lipid droplet surface recruit the mitochondria and help to prevent direct exposure of non-esterified fatty acid to cellular system which causes direct lipotoxicity to cells [49, 76]. Moreover, it is also reported that Peroxisome proliferator-activated receptor (PPAR)-alpha (PPAR-α) majorly involved in regulation of expression of PLIN5 in oxidative tissues [77–80].

Currently, reported *in-vivo* and *in-vitro* studies suggest that PLIN 5 overexpression was highly observed in oxidative tissues. So, Lipid droplets are stores the neutral lipids such as retinyl ester, cholesterol ester and triacylglycerol which reduce the cellular load of fatty acid here PLIN 5 expression on lipid droplets surface and recruits the mitochondria, so lipid droplets channelling the free fatty

acid to directly mitochondria and increase the beta oxidation and another function of PLIN5 stabilize the lipid droplets which prevent the lipolysis of lipid droplets from ATGL this action helps in storage of excessive fat from cells into lipid droplets which give cytoprotective action of cells from direct lipotoxicity [49, 76]. Recently, in-vitro studies proved that lipid droplets containing triglycerides are resistant to lipolysis by lipases enzyme when cells are treated with PLIN5 expression, so it proved that PLIN5 highly involved in the lipid droplet stabilization [76].

Reported data suggest that steatosis conditions was not much affected due to overexpression of PLIN5 but fatty acid exposures on cells are reduced due to recruitments of mitochondria on lipid droplets and stabilization of lipid droplets which prevent direct lipotoxicity of cells [49, 76].

Lipid droplets are commonly present in all cellular organism and maintain the lipid homeostasis condition at normal level. Recent finding demonstrated that PLIN5 also associated with hepatic stellate cell activation from quiescent state because some study indicates that knock out PLIN5 mouse shows hepatic stellate cell activation and with high fat diet increase the level of lipotoxicity after a certain periods which shows massive destruction of lipid droplets and decrease the expression of PLIN5 [81]. Another findings define that the possible role of PLIN 5 after deletion of PLIN5 in high fat diet model further shows destruction of hepatocytes with hepatotoxicity [82]. Hepatic stellate cells are majorly involved in case of fatty liver diseases and activation of hepatic stellate cell increase the expression of extracellular matrix protein such as alpha-smooth muscle actin, collagen1 and collagen3 expression which further disease progression leads to liver fibrosis [83]. Myofibroblasts are understand the major source of extracellular matrix protein expression which is derived from the bone marrow fibrocytes and hepatic stellate cells [83].

Mechanistic approach of perilipins for fat regulation

Upon mechanistic view, PLIN1 expression has been observed in hepatosteatotic condition and knock out PLIN1 rodent's studies claimed that improvement in steatosis. Somewhere clinical findings hypothesized that it can be proved as a potential anti-obesity therapeutic targets.

Comparative gene identification 58 (CGI58) is another cofactor for PLIN1 which is bounded with PLIN1 and inhibit the lipolysis via lipase enzymes but after Protein Kinase A activation PLIN1 and other perilipins phosphorylation happened and translocate the HSL into lipid droplets and CGI58 detach from phosphorylated perilipins and bound with ATGL as an activator increase the directly lipolysis rate [84–87]. Another side G0/G1 gene deactivate the activity of ATGL and reduce the lipolysis [88, 89]. However, CGI58 is important regulator of lipolysis process using a binding site on ATGL and other Perilipins like PLIN1, PLIN2 and PLIN5 surface protein of lipid droplets. The store triacylglycerol into lipid droplets converted into fatty acid and glycerol via activation of ATGL, and this fatty acid directly exposed to cellular systems and leads to major lipotoxicity. Exact role of perilipins and CGI58 and involvement of ATGL and HSL are still unclear. CGI58 mutation or their deficiency decrease the lipolysis of triglycerides and increase the accumulation of neutral lipids that shows chronic steatosis [90, 91]. Further studies can be improve a better approach to clear the mechanism of perilipins and lipase system involved in metabolic disorders.

CIDEC or FSP27 is another protein which is expressed highly in hepatic steatosis condition somewhere knock out FSP27 claimed that decrease in fatty load and observed improvement in steatosis conditions. FSP27 have a dominant role in LD-LD fusion process and adipose tissue differentiation [92, 93]. We have to target another parameters also which is shows exact mechanism of FSP27 in metabolic disorders or fat accumulation.

Perilipin2 is highly expressed in adipocytes and majorly expressed during adipocyte differentiation process. Surprisingly nascent lipid droplets during the time of detachment from ER expressed PLIN3, PLIN4 and PLIN5 but in mature stage these perilipins are replaced by PLIN2. Knock out study of PLIN2 mice shows significant reduction in accumulated fat.

PLIN2 knock out studies also claimed that impairment in SREBP2 signalling which involved in the de-novo lipogenesis. PLIN2 and CIDEB involved lipidation process and formation of VLDL assembly through VLDL transport vesicle [66].

PLIN3, PLIN4 and PLIN5 expressed by nascent lipid droplets which consist newly synthesized triacylglycerol's but apart from other perilipins PLIN3 have lack of PAT domain, and recent studies shows that involvement in inflammation cascade, however, downregulation of PLIN3 reduces the expression of PGE2 production still their major mechanism of action is unclear.

PLIN5 among all perilipins closely linked with mitochondria after physical exercise PLIN5 recruits mitochondria and increase neutral lipids transport to mitochondria to decrease the fatty load.

PLIN5 overexpression shows downregulation of lipase activity and decrease direct exposure of fatty acids and cellular lipotoxicity in fatty cardiac or cardiac steatosis condition but steatosis condition is not significantly reduced.

In this review, we focussed on possible role of all perilipins involved in lipid droplets biogenesis and metabolic

disorder with specially focus on NAFLD. If we focussed on these family proteins it can be proved good approach to cure the fatty liver disease in future prospectives.

Conclusions

Lipid droplets associated proteins can be a better potential target to combat the fatty liver disease. Perilipins PLIN3 and PLIN5 are less studied that further experimental proves are needed to clarify the involvement in disease pathogenesis. Based on revealed data, overexpression of perilipins inhibits the inflammatory cytokines which mechanism followed is still unclear that it can be good study to evaluate the signalling between Perilipins and cytokines. CIDEB, CIDEC, CGI58 and their involvement in disease pathogenesis also a good approach to understand the lipid droplet biogenesis and their role in metabolic disorders.

There are lack of study done on how after physically exercise and in fasting state PLIN5 recruits number of mitochondria, so we have to manipulate exact functioning and cell signalling happened between lipid droplets associated proteins PLIN5 and mitochondria.

Overall study about lipid droplets from synthesis in ER to distribution in cytosolic and distribution to different part of the body varies associated protein levels and functionally different. So, this review focussed on mainly in perilipins family proteins which is show eminent role in all metabolic disorders.

Abbreviations

ATGL: Adipose triglycerides lipase; CIDE: Cell death inducing DFF45-like effector; CGI58: Comparative gene identification 58; DGAT: Di-acyl glycerol's acyl transferase; FSP27: Fat specific protein 27; GPAT: Glycerol-3-phosphate acyltransferase; PLIN: Perilipin; NAFLD: Non-alcoholic fatty liver disease; PAT domain: Perilipin, ADPH, TIP47 domain; PGE2: Prostaglandin E2; ER: Endoplasmic reticulum; ROS: Reactive oxygen species; SREBP: Sterol regulatory elementary binding protein; TIP47: Tail interacting protein 47; VLDL: Very low density lipoprotein.

Acknowledgements

This article supported by National Institute of Pharmaceutical Education and Research, Kolkata (NIPER-K).

Authors' contributions

All authors have read and approved the final manuscript. AS Author participated in study conception and writing a manuscript. AS Author participated to draft the manuscript. AS Author give final approval of the version to be submitted and any revised version.

Funding

The author received no financial support for publication of this article.

Availability of data and materials

Data and materials are available upon request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The author declare that they have no competing interests.

Received: 13 May 2021 Accepted: 22 December 2021
Published online: 04 January 2022

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