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Organelles in focus

Lipid droplets and their interactions with other organelles in liver diseases

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ABSTRACT

Lipid droplets are cellular organelles used for lipid storage with a hydrophobic core of neutral lipids enclosed by a phospholipid monolayer. Besides presenting as giant single organelles in fat tissue, lipid droplets are also widely present as a multitude of small structures in hepatocytes, where they play key roles in health and disease of the liver. In addition to lipid storage, lipid droplets are also directly involved in lipid metabolism, membrane biosynthesis, cell signaling, inflammation, pathogen-host interaction and cancer development. In addition, they interact with other cellular organelles to regulate cellular biology. It is fair to say that the exact functions of lipid droplets in cellular physiology remain largely obscure. Thus prompted, here we aim to analyze the corpus of contemporary biomedical literature to create a framework as to how the role of lipid droplets in hepatocyte physiology and pathophysiology should be understood. The resulting framework should help understanding the interaction of lipid droplets with other organelles in important liver diseases, including fatty liver disease, viral hepatitis and liver cancer and direct further research directions.

1. Introduction

Lipid droplets (LDs) are specialized cellular organelles that are present in many types of cells and tissues mediating lipid storage (Murphy, 2001). Although diverse in morphology, LDs are universally characterized by the presence of a hydrophobic core that mainly consists of triacylglycerols and sterol esters and other neutral lipids, encapsulated by a phospholipid monolayer that contains integral and peripheral proteins (Fig. 1). Initially, LD function was thought to be limited as a passive reservoir for lipid storage, but an increasing body of research shows that the surface proteome of LDs allows them to actively participate in a variety of cell biological functions (Fig. 1). Accordingly, LDs are now recognized as dynamic hubs in lipid metabolism, energy homeostasis and cellular signaling (Sanjabi et al., 2015). Although much of the mechanistic details remain largely obscure, it is evident that many of these functions are exerted through interactions of LDs with other organelles (Guo et al., 2009).

Because of drastic changes in life style and environment, obesity has grown into a global pandemic during the past decades. The increase in obesity is accompanied by a plethora of comorbidities, in particular insulin resistance, type 2 diabetes mellitus, hypertension, cardiovascular disease and dyslipidemia. Thus, research on LDs mainly focused on fat cells of the adipose tissue, which is the largest energy reservoir of the body. It is important to note, however, that the liver controls lipid metabolism in the body, and lipid metabolism dysfunction is universally associated with hepatic physiopathology (Gluchowski et al., 2017). Liver cells contain many LDs, and LDs in these cells are subject to interaction with other cellular organelles including endoplasmic reticulum (ER), mitochondria, peroxisomes and lysosomes (Olzmann and Carvalho, 2019). In this review, we aim to analyze the role of LDs in hepatocyte physiopathology, focusing on their multifaceted interactions with other cellular organelles in the context of the most important liver diseases.

2. The interactions between lipid droplets and other organelles

The notion that LDs may have a more profound action in cellular physiology apart from their role as a lipid reservoir comes from the realization that LDs directly interact with other cellular organelles. In turn, this insight was driven by the development of novel imaging technologies that allow direct visualization of the physical interactions between LDs with other organelles in living cells (Fig. 2). A variety of interactions have now been described, in particular between LDs and ER, mitochondria, peroxisomes or lysosomes, respectively. As it will become clear below, LD-ER and LD-mitochondrion interactions play the most prominent roles in development and progression of liver diseases.

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2.1. LD-ER interaction

The ER is responsible for LD generation. Neutral lipids, which form the core of LDs, are synthesized in the ER and are subsequently packed in a phospholipid monolayer after which the nascent organelles may bud from the ER into the cytosol in a multistep process (Tauchi-Sato et al., 2002). Depending on the exact phospholipid composition and resulting surface tension, LDs of different sizes are formed, while final release from the ER requires surface protein loading of the LDs (Chorlay et al., 2019). Protein translocation from the ER membrane to LDs requires such proteins to have a hydrophobic hairpin structure. Importantly, however, LDs often do not dissociate at all but remain associated to the ER. Indeed, in yeast LDs universally appear connected to the ER membrane (Jacquier et al., 2011). Using spectral imaging of monkey COS-7 cells, 85 % of LDs were estimated to be in physical contact with the ER (Valm et al., 2017). Such association may facilitate recycling of LD components. If cellular metabolic need requires lipid mobilization, the level of neutral lipids presents in LDs will decline. Some integral droplet proteins such as AAM-B and UBXD8 will then return back to the ER (Zehmer et al., 2009), while other proteins are transported to the Golgi complex (Olofsson et al., 2009). Yet other LD proteins are degraded via ubiquitin-proteasome system or autophagy (Bersuker and Olzmann, 2017). Seipin is stably associated with nascent ER-LD contacts (Salo et al., 2016), which supports the formation of ER-LD contacts and promotes delivery of triacylglycerols from ER to LDs (Salo et al., 2019). Thus overall, LDs appear to be dynamic structures and their constituents can enter a multitude of other subcellular compartments.

The ER is very sensitive to changes in the intracellular environment, if such changes provoke accumulation of unfolded or misfolded proteins in ER and unfolded protein response (UPR) ensues. The presence of a UPR is implicated in many diseases (Tschurtschenthaler et al., 2017) involving a highly ordered signal transduction cascade that includes IRE1, PERK and ATF6, and results in either a return to ER homeostasis or induction of programmed cell death (Walter and Ron, 2011). An evolutionary conserved effect of the UPR is the induction of LD formation (Fei et al., 2009; Rutkowski et al., 2008). This may be a consequence of metabolic reprogramming following activation of the UPR, which involves downregulation of many metabolism-related genes including transcription factors and thus promotes lipid accumulation in the liver (Oyadomari et al., 2008; Rutkowski et al., 2008). In turn, LDs can take up unfolded and misfolded proteins from the ER and hence alleviate ER stress (Ploegh, 2007). Thus, LDs actively contribute to appropriate functioning of the ER.

2.2. LD-mitochondrion interaction

Besides the ER, mitochondrion is also a prime target for interaction with LDs (Wang et al., 2013). In mammalian cells, lipolysis of LD-derived fatty acids takes place in mitochondrion through β-oxidation (Shaw et al., 2008; Tarnopolsky et al., 2007). During nutrient starvation, LD-derived lipids are necessary for ATP production and accordingly LD-mitochondrion interactions are induced in an AMPK activation-dependent process (Herms et al., 2015). Direct connections between LDs and mitochondria are required to enable flux of fatty acids into mitochondria (Rambold et al., 2015).

Based on LD-interaction status, mitochondria can be divided into two subpopulations, peridroplet mitochondria that binds to LDs and cytoplasmic mitochondria, with distinct role in lipid metabolism (Benador et al., 2019). Peridroplet mitochondria have a distinctive protein composition and structure reflecting their role in lipid metabolism, supporting both triacylglycerol synthesis and β-oxidation (Benador et al., 2018). Important in LD-mitochondrion interaction is the perilipin protein family. They act as surface scaffolds and regulators in LDs (Wang and Sztalryd, 2011). The members of perilipin family interact with

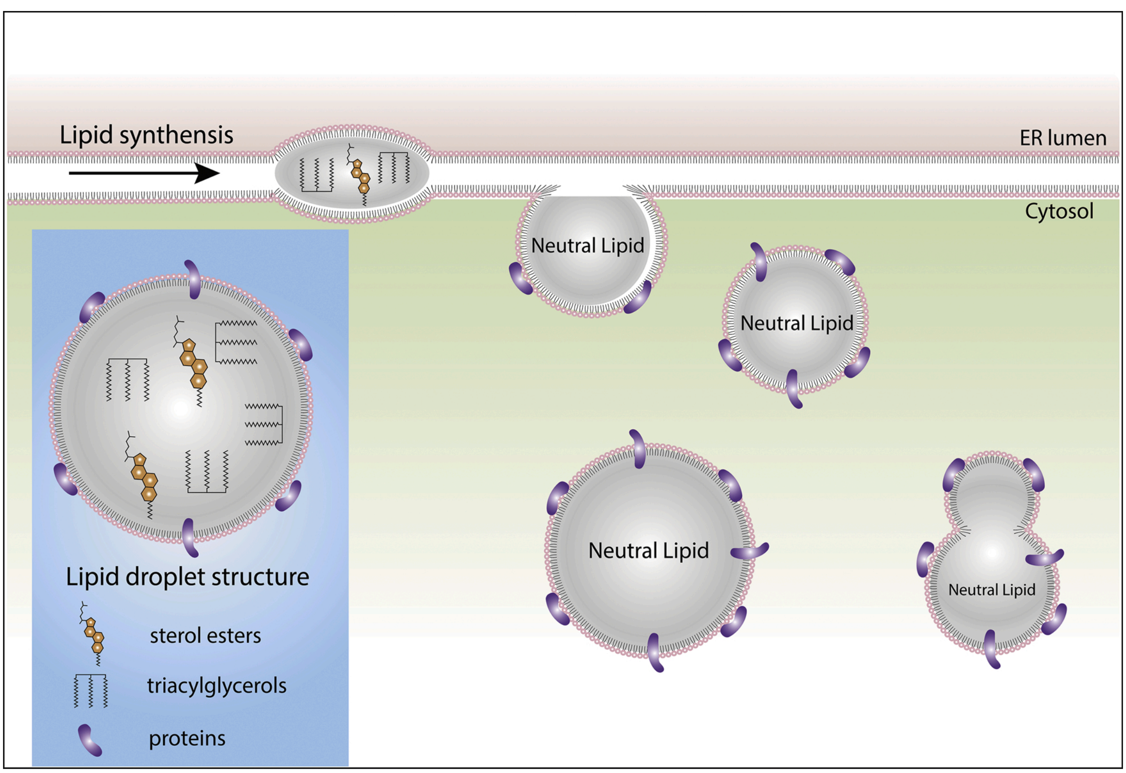

Fig. 1. The structure and biogenesis of lipid droplets. Lipid droplet (LD) has a hydrophobic core with neutral lipids, consisting of triacylglycerols (TAGs) and sterol esters, encircled by a phospholipid monolayer with integral and peripheral proteins. The classical hypothesis of LD biogenesis is based on ER-budding model. TAGs and sterol esters are synthesized in the ER. With increasing neutral lipid accumulation, lens will grow and bud into a nearly spherical droplet from ER membrane. Subsequently, proteins from ER bilayer and cytosol translocate to LD surface. Through new fatty acids synthesis and LD fusion or coalescence, LDs will grow into different sizes.

mitochondrion to exert functions in lipid metabolism. In mammals, this function is mediated by Perilipin 5 (Plin5) which recruits mitochondria to the LD surface through its C-terminal region but concomitantly protects the mitochondrion from excessive fatty acid exposure by regulating LD hydrolysis and controlling local fatty acid flux (Wang et al., 2011). In addition to lipid metabolism regulation and lipotoxicity defense, Plin5 also has antioxidant role to alleviate oxidative damage, whereas oxidative stress is intimately associated with mitochondrial electron transport chain (Zhu et al., 2020).

Some aspects of LD-mitochondrion interactions also involve ER. Calcium (Ca^{+}) is an important intracellular second messengers stored in the ER (Van Den Brink et al., 1999). In mammalian models, LDs mediate Ca^{+} signal transduction from the ER to the mitochondrion (Bush et al., 1992; Greineisen et al., 2014). Another example is MIGA2, an outer mitochondrial membrane protein that links mitochondria to LDs, but also binds to the membrane proteins VAP-A or VAP-B of ER. Through multifaceted links among mitochondria, ER and LDs, MIGA2 promotes *de novo* lipogenesis from non-lipid precursors and stores lipids in LDs (Freyre et al., 2019). Hence, LDs are an essential component in the joint regulation of cellular metabolism by the ER and the mitochondrial compartment.

2.3. LD-peroxisome interaction

Peroxisomes are membrane-bound organelles present in the cytoplasm of all eukaryotic cells. They are essential in metabolism of lipids and reactive oxygen species. In the liver, peroxisomes also catabolize bile acid intermediates. Both LDs and peroxisomes are formed in the ER. This is thought to occur at the same ER subdomains where the reticulon homology domain of the multiple C2 domain containing transmembrane protein is located. This suggests that an intimate interactions between LDs and peroxisomes may exist, as both organelles are generated at the same location and both have an important role in cellular lipid metabolism (Joshi et al., 2018). An obvious example of LD-peroxisome interaction functionality is the β-oxidation of fatty acids. This crosstalk links lipolysis mediated by LDs to catabolize fatty acid β-oxidation within the peroxisomes (Shai et al., 2016), which likely involves trafficking of proteins and lipids between these organelles and the mitochondrion (Joshi and Cohen, 2019). Experimental demonstration of the interactions between LDs, peroxisomes and mitochondria and its role in regulation of energy consumption has been reported in murine adipocytes involving the CIDE-ATGL-PPARα pathway (Zhou et al., 2018). Thus a picture emerges that around the LD a metabolic niche is generated that coordinates cellular lipid metabolism.

2.4. LD-lysosome interaction

Lysosomes are important for cellular waste disposal and accordingly contain a variety of enzymes that enable the digestion of biomolecules including lipids. Lysosomes are closely linked to LD catabolism. Although LD catabolism is most directly linked to lipolysis, LDs can also be subject to autophagy. Conversely, degradation of cellular components by lysosomes may increase availability of triacylglycerol and thus necessitate LD formation (Singh et al., 2009). In the liver, involvement of autophagy in lipid catabolism is most prominent during fasting or nutrient deprivation, although lipophagy also maintains constitutive lipid degradation. Lysosomes regulate lipid metabolism through autophagy, and inhibiting autophagy can increase the amount of triacylglycerols and LDs (Singh et al., 2009). LDs provide lipid precursors for autophagosome biogenesis, more specifically for autophagosomal membrane formation (Settembre and Ballabio, 2014). Furthermore, the ER can also contribute to the interactions between LD and autophagy (Velázquez et al., 2016).

3. Lipid droplets and their interactions with other organelles in major liver diseases

Dysregulation and imbalance of lipid metabolism in the liver inevitably cause pathogenesis. The most prominent disorder in this respect is fatty liver disease. Fatty liver disease is a leading etiology of primary liver cancer, and altered hepatic lipid metabolism can fuel hepatic carcinogenesis providing a direct link between LDs and liver cancer (Fig. 3). In addition, intracellular pathogens, including hepatitis viruses, can exploit LDs to sustain their life cycle. Lipid metabolism is a

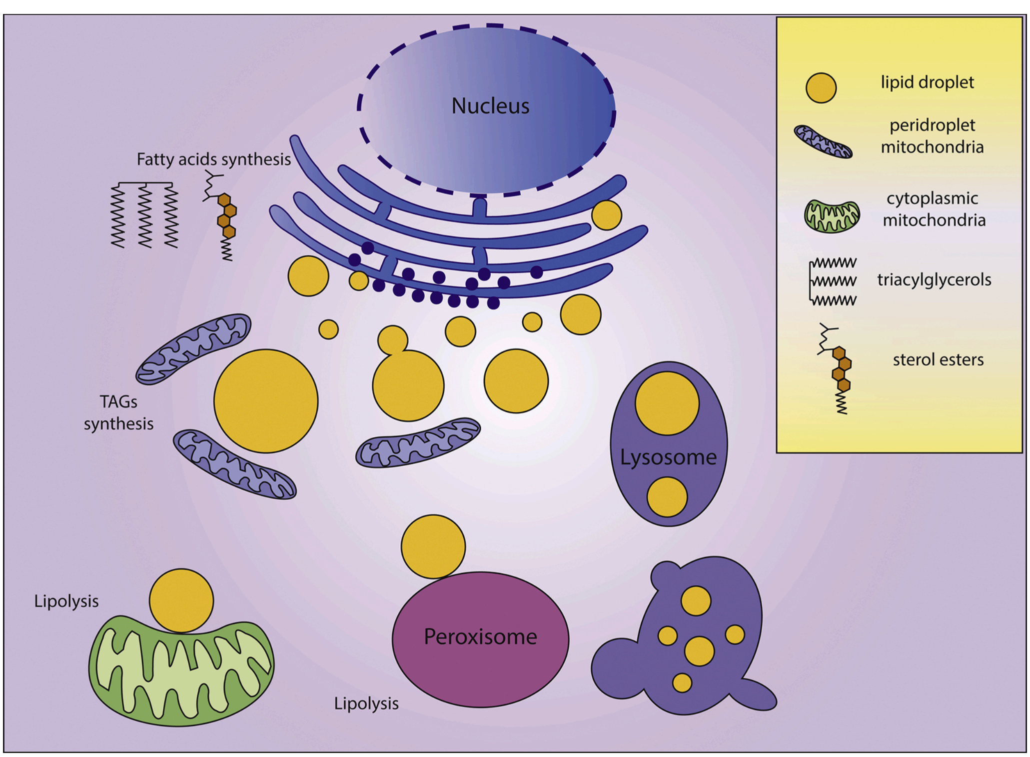

Fig. 2. Interactions between lipid droplets and other cellular organelles. ER is the place to form LDs, and LD-ER contacts transport lipids and proteins. Mitochondria can be divided into two subpopulations: peridroplet mitochondria that bind to LDs support triacylglycerol synthesis and conversely reduce β-oxidation activity, and cytoplasmic mitochondria that take place lipolysis to supply energy. Peroxisomes exert lipolysis through catabolization of fatty acid β-oxidation. Lysosomes degrade fatty acids through autophagy. ER: endoplasmic reticulum; LDs: lipid droplets.

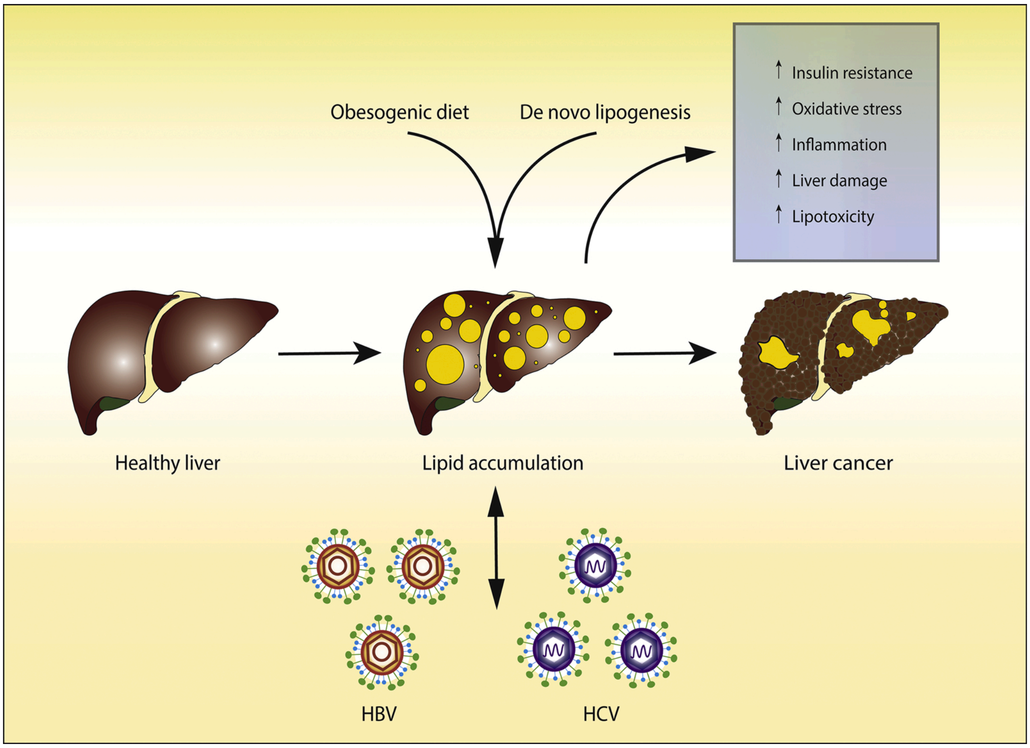

Fig. 3. Lipid droplets in major liver diseases. Excessive fatty acids lead to lipid metabolic disorder. Imbalance of lipid homeostasis will trigger LD formation that promotes development of metabolic dysfunction-associated fatty liver disease. Similarly, hepatitis virus infections, especially HBV and HCV, accelerate lipid accumulation and cause inflammation in the liver. In turn, LDs support the life cycle of hepatitis viruses. Fatty acids sustain HCC cell growth and create a supportive microenvironment for cancer stem cells. LDs: lipid droplets; HBV: hepatitis B virus; HCV: hepatitis C virus; HCC: hepatocellular carcinoma.

complicated process involving many different organelles to maintain the balance. Imbalance of lipid homeostasis will cause damage to organelles and promote disease progression.

3.1. Metabolic dysfunction-associated fatty liver disease

Metabolic dysfunction-associated fatty liver disease (MAFLD) is under the new nomenclature for pathology previously referred as non-alcoholic fatty liver disease (NAFLD). MAFLD is defined as hepatic steatosis in conjunction with at least one of three conditions, including overweight/obesity, presence of type 2 diabetes mellitus, or evidence of metabolic dysregulation (Eslam et al., 2020). Although the precise epidemiology of MAFLD remains unknown as a new terminology, the prevalence of NAFLD has been estimated to be 25 % of the global population (Younossi et al., 2016).

Steatosis may present as either microvesicular or macrovesicular LDs in hepatocytes and is the hallmark of fatty liver disease. Fatty acids in the liver are derived from diet uptake, *de novo* lipogenesis and endogenous lipid catabolism. Imbalance in lipid anabolism and catabolism causes excessive fatty acid storage in hepatocytes as LDs, promoting the development of fatty liver disease. Fatty acids can also be converted to lipid intermediates that impair insulin signaling, referring as lipid-induced insulin resistance and lipotoxicity. Accumulated LDs will trigger further hepatic oxidative stress and inflammation, resulting in continued liver damage and more advanced disease stage such as steatohepatitis (Chen et al., 2019).

Disease progression of MAFLD involves the interactions between LDs and other organelles. Hepatic steatosis progresses to steatohepatitis often accompanied by ER stress, and mitochondrial and lysosomal dysfunctions. Activation of cell stress pathways and impairment of organelle functions play important role. Disorder of lipid metabolism causes chronic ER stress in the liver via disruption of calcium homeostasis, and ER stress in turn induces LD formation and hepatic steatosis (Fu et al., 2011; Yamamoto et al., 2010). PLIN2 is a LD-associated protein that provides reciprocal stabilization to LDs, and its expression is positively correlated to mitochondrial activation (Xu et al., 2019).

LD-associated proteins are also important for MAFLD progression. The PAT family proteins located on LD surface include perilipin, adipophilin, TIP47, S3-12 and OXPAT. They are differentially expressed in fatty compared to normal liver. Perilipin, adipophilin and TIP47 are associated with different LD sizes. TIP47 affects nascent LDs, while perilipin and adipophilin are important for maturation and maintenance of LDs in human hepatocytes (Straub et al., 2008). CIDEA and Fsp27 are LD-associated proteins that promote LD fusion and regulate lipid storage. Their expression is dramatically upregulated in hepatic steatosis (Zhou et al., 2012). This process may be mediated by MKP5. Because loss of MKP5 in mice activates p38, resulting in increased expression of CIDEA and Fsp27 (Tang et al., 2019). 17β-hydroxysteroid dehydrogenase-13 (17β-HSD13), a newly identified LD-associated protein, has been demonstrated as a pathogenic protein in MAFLD. 17β-HSD13 controls the number and size of LDs and is causative for fatty liver phenotype (Su et al., 2014). High expression of 17β-HSD13 in fatty liver has been shown to be induced by liver X receptor α through SREBP-1c in mouse model (Su et al., 2017).

3.2. Alcoholic liver disease

Alcoholic liver disease (ALD) is one type of epidemic chronic fatty liver disease worldwide. Accumulation of LDs is a common feature in both MAFLD and ALD, but chronic alcohol consumption results in some unique characteristics of ALD.

Alcohol intake can induce LD accumulation and alter LD properties to induce macrosteatosis (Orlicky et al., 2011; Valcin et al., 2020). Except direct effects on LD accumulation, alcohol and its metabolite, acetaldehyde, indirectly induce LD generation through damage of other organelles. They can decrease mitochondrial β-oxidation, impair lysosome biogenesis and increase cholesterol level by inducing ER stress that leads to mitochondrial impairment (Chao et al., 2018; Farfán Labonne et al., 2009; Lluis et al., 2003). LD motility maintaining the interactions with other organelles relies on cytoskeletal motors (Kilwein and Welte, 2019). Alcohol induces microtubule acetylation, which impairs LD motility and accumulation of large, immobile LDs in the liver (Groebner et al., 2019). Thus, alcohol-induced lipid deposition decreases LD motility and prevents active communications with other organelles.

3.3. Viral hepatitis

Viral hepatitis can be caused by the five hepatotropic viruses including hepatitis A, B, C, D and E. Globally, about 500 million people are chronically infected with hepatitis B (HBV) or C (HCV) virus. The link of HBV to LDs is mainly through the viral HBx protein, which causes lipid accumulation by upregulation of the liver X receptor and its lipogenic target genes (Kim et al., 2007; Na et al., 2009). HBV viral particle production has been shown to impair LD expansion associated with inhibition of the expression of CIDE proteins in cell culture models. Because CIDE proteins support HBV production; this may serve as negative feedback loop for maintaining persistent infection (Yasumoto et al., 2017).

HCV is the best known pathogen with close connections to LDs. LDs serve as putative sites for viral assembly during HCV replication (Miyanari et al., 2007). The process of infectious HCV particle assembly consists of nucleocapsid formation, budding into the ER, and virion maturation. The capsid Core protein closely associates with LDs, and further recruits nonstructural proteins around LDs to participate in virus production (Miyanari et al., 2007). HCV assembly likely takes place at the sites requiring interactions of ER and LDs (Filipe and McLauchlan, 2015). A recent high-resolution imaging study in cell culture models indicates selective recruitment of ER membranes wrapping LDs to form membranous structure coupling HCV replication and assembly (Lee et al., 2019). HCV infection also causes ER stress and leads to Ca^{2+} release from ER to mitochondria resulting in mitochondrial dysfunction. This triggers oxidative stress, lipogenesis and decreased oxidative phosphorylation (Scrima et al., 2018). HCV Core protein can also be efficiently targeted to LDs outside the context of virion assembly, and induce LD redistribution and hepatic steatosis (Boulant et al., 2008; Camus et al., 2014). This partially explains why MAFLD is a prominent feature of chronic hepatitis C patients, and eradication of HCV by antiviral treatment dramatically decreases liver steatosis (Tada et al., 2018).

3.4. Liver cancer

Fatty liver disease and viral hepatitis are the leading etiologies of primary liver cancer, namely hepatocellular carcinoma (HCC). Enhanced lipogenesis is a metabolic hallmark of cancer cells, and aberrant lipid metabolism universally occurs in HCC cells (Hu et al., 2020). Fat-containing liver lesions are commonly seen in HCC patients (Balci et al., 2009). In HCC, lipogenesis pathway is over-activated, while fatty acid oxidation is concomitantly downregulated (Björnson et al., 2015; Yamashita et al., 2009). Specific to the high rate of tumor growth, HCC cells require fatty acids to support their proliferation (Menendez and Lupu, 2007). Hypoxia is a common feature in liver cancer development. Hypoxia inhibits mitochondrial activity and ROS accumulation through HIF/HEY1/PINK1 pathway (Kung-Chun Chiu et al., 2019). Under hypoxic conditions, LD catabolism is inhibited by ATGL, the rate limiting lipase in lipolysis, leading to LD accumulation, and thus adapting cellular metabolism and provoking resistance to programmed cell death (Munir et al., 2019; Zhang et al., 2017).

Recent evidence indicates the essential involvement of lipid metabolism in cancer stem cells (CSCs). Activation of intrinsic lipid pathways in CSCs upregulates fatty acid *de novo* synthesis (Yasumoto et al., 2016). Furthermore, the lipid context in tumor microenvironment, in particular the stem cell niche, regulates CSC behavior (Nieman et al., 2011). Liver tumors are known to harbor CSCs (Cao et al., 2020), and the role of LDs and lipid metabolism in this unique cancer cell population deserves to be further studied.

4. Conclusion

The liver is a central organ in lipid metabolism and LDs are widely present in hepatocytes. LDs play key roles in health and diseases of the liver, involving in lipid metabolism, energy homeostasis, cell signaling, inflammation, pathogen-host interaction and carcinogenesis. LDs are highly dynamic organelles closely associated and interacting with other cellular organelles. The presence of LDs and their interactions with different organelles has been widely observed in different liver diseases. However, there remain many knowledge gaps in understanding the implications of these interactions. The exact biological functions of different interactions between LDs and specific organelles are still largely elusive. The mechanisms that regulate these dynamic interactions have hardly been revealed. Thus, mechanistically deciphering the role of LDs and their interactions with other organelles in the liver shall help to better understand the pathogenesis of major liver diseases including MAFLD, viral hepatitis and cancer, as well as to facilitate therapeutic development.

Declaration of Competing Interest

The authors declare that no competing interests exist.

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