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Dysfunctional Lysosomes Contribute to Lipid Droplet Accumulation in Fatty Liver Disease

Fatty liver disease

Heavily vascularized, the liver plays a pivotal role in detoxifying blood and is responsible for the breakdown of fat within the small intestines. The liver cells themselves, known as hepatocytes, carry out numerous biochemical functions including cholesterol synthesis, lipogenesis and triglyceride production. Defects in fatty acid metabolism can lead to fatty liver disease (FLD), a disease where excess fat will build up in the liver.[1] If fatty liver disease is not diagnosed and treated in an early stage, a cascade of structural changes will occur inside the liver. During the first phase of FLD there will be an increase in lipids depositing in lipid droplets of hepatocytes. The lipid droplets will grow, expand and accumulate, leading to and enlargement of the liver. This in turn will lead to scar tissue formation followed by fibrosis. Consequently, the scar tissue makes the liver stiff and hard, leading to cirrhosis and ultimately liver failure. Following, we will discuss lipid droplets, their pivotal role in FLD, and recent interest in the lysosome's role in FLD.

Lipid accumulation in lipid droplets

Lipid droplets are small, spherical structures found within most cells and are composed of a core of neutral lipids, such as triacylglycerides, surrounded by a phospholipid monolayer. They play a critical role in the storage and metabolism of fats in the body. In the liver, the lipid droplets are important for the fats' synthesis, storage and breakdown. Under normal conditions, the liver synthesizes and stores triacylglycerides, which are then released into the bloodstream during periods of fasting or when the body needs energy.[2]

In the healthy liver, there is constant maintenance of incoming and outgoing lipids. Lipids are acquired through the uptake of circulating lipids via fatty acid transporters CD36, FATP2 and FATP5.[2,3] Moreover, lipids can be generated via de novo lipogenesis inside the hepatocytes mediated by SREBP1c and ChREBP. Subsequently, lipids are disposed through oxidation mainly in mitochondria and partly in peroxisomes and cytochromes. In addition, lipids can be exported out of the liver in very low-density lipoproteins (VLDL) to be used in other tissues. Lipid export is regulated by MTTP and apoB100.[3] These four mechanisms: lipid import, lipogenesis, lipid metabolism and lipid export are tightly regulated inside the hepatocytes to maintain healthy lipid levels.

In the first stage of FLD, there is a dysfunctional lipid metabolism leading to the accumulation of lipids in lipid droplets. Dysregulation of the aforementioned mechanisms are in part responsible for onset of FLD. In FLD, an increase of transmembrane proteins CD36, FATP2 and FATP5 enhances uptake of circulating lipids.[4] Similarly, an increase of SREBP1C is often found, thereby increasing de novo lipogenesis and hepatic lipid levels.[5] In other cases, mitochondrial defects lead to dysfunctional lipid metabolism and increased cytochrome and peroxisome lipid oxidation.[6] This in turn increases the levels of reactive oxygen species (ROS) which promotes oxidative stress and leads to cellular damage. Moreover, decreased levels of MTTP and apoB100 decrease the amount VLDL export.[6] As a net result of dysregulation in these pathways, lipids accumulate inside the hepatocytes in lipid droplets. In this vicious circle, more oxidative stress is generated by ROS leading to more liver damage, advancing FLD to cirrhosis.

Currently, researchers are very interested in visualizing these lipid droplets and the expansion of the lipid droplet itself. Using fluorescent dyes, it is possible to stain the lipid droplets, and quantify expansion and accumulation.[7] Using these techniques, it is clear that in FLD, lipid droplets expand and accumulate inside the hepatocytes, indicating a dysfunction in lipid level homeostasis. These novel techniques make it possible to better understand the mechanisms involved in lipid droplet accumulation.[8]

Lysosomal regulation of lipid droplets.

Lysosomes are membrane-bound, spherical organelles that contain hydrolytic enzymes involved in metabolism of different kinds of biomolecules. Having more than 60 enzymes in the lysosomal lumen, the lysosome can break

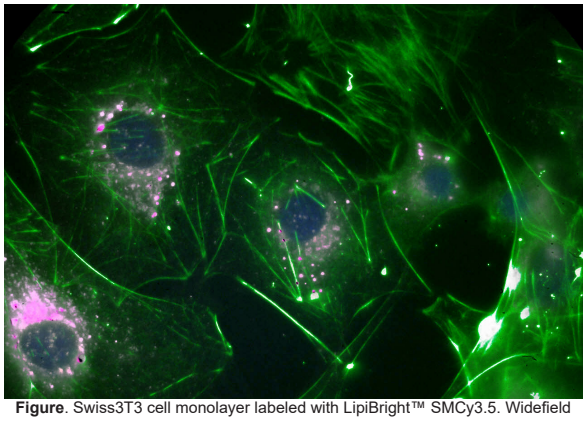

Figure. Swiss3T3 cell monolayer labeled with LipiBright™ SMCy3.5. Widefield fluorescent imaging of live Swiss3T3 labeled with LipiBright™ SMCy3.5 (Pink), a live cell actin cytoskeleton stain (Green, SiR-Actin), and a live cell DNA probe (Blue, SPY505-DNA).

Lipid Staining PRODUCTS

Continued from Page 1

down most biomolecules including peptides, nucleic acids, carbohydrates and lipids. In addition to biomolecule breakdown, the lysosomes are involved in autophagy, nutrient sensing, signaling, and gene regulation. This allows the lysosome to regulate metabolism at different levels.[9]

In the liver, the lysosome degrades lipids and sends the degradation products to mitochondria and peroxisomes to be oxidized.[10] In addition, the degradation products regulate mTOR pathway activation.[11] The mTOR pathway is a signaling pathway that plays a key role in regulating lipid metabolism. When stimulated by the lysosomal degradation products, It will promote lipogenesis through the activation of lipogenic enzymes and inhibit lipid metabolism by suppressing lysosomal function.[12] Therefore, the lysosome – mTOR axis creates a cycle that regulates both anabolism and catabolism of lipids inside hepatocytes. During FLD, increased lipid levels stimulate the mTOR pathway, exacerbating lipogenesis and decreasing lysosomal lipid metabolism.[13] This leads to a vicious cycle that results in lipid accumulation in the lysosomes, leading to dysfunctional autophagic turnover of the lipid droplets by lysosomes which worsens the hepatic steatosis.[14] Furthermore, using lipid droplet dyes, lipid droplets were found to interact with lysosomes.[15] In healthy cells, the lipid droplets are gradually broken down by transporting free fatty acids out of the lipid droplets and into the cytosol to be metabolized. As the lipid droplets are broken down, they become small enough to be engulfed by autophagosomes that will transport the lipid droplet to lysosomes for complete degradation. This way, the lysosomes play a crucial role in the breakdown and removal of excess lipid droplets in the liver. However, in individuals with FLD, the lysosomes will be overwhelmed with fatty acids and lipid droplets to the point where they are unable to effectively break down and remove lipid droplets. Therefore, the lipid-droplet-autophagosome-lysosome axis contributes to fatty liver disease.[16]

Due to these recent findings of the involvement of lysosomes in lipid droplet accumulation during fatty liver disease, the lysosome is seen as a potential new target to treat or prevent fatty liver disease. By inhibiting the mTOR pathway the normal functioning of the lysosome and therefore autophagy can be restored.

Conclusions & outlook

Fatty liver disease is a prevalent disease with a clear mechanism of onset. The pathways of lipid metabolism are highly regulated and interconnected. An imbalance in any of these pathways can significantly alter lipid catabolism and anabolism, leading to a build-up of lipids within hepatocytes. Lysosomal waste products stimulate the mTOR pathway which is a crucial regulator of both anabolism and catabolism of lipids; furthermore, the lysosomes break down lipid droplets and decrease the lipid droplet size by metabolizing free fatty acids. Lysosomal contribution to lipid metabolism has long been under-investigated; however, recent findings suggest they play a significant role in the onset of FLD and could be useful in the future as a novel therapeutic target.

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Lysosome Probes

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