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Review

Recent insights into the molecular pathophysiology of lipid droplet formation in hepatocytes

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ABSTRACT

Triacyglycerols are a major energy reserve of the body and are normally stored in adipose tissue as lipid droplets (LDs). The liver, however, stores energy as glycogen and digested triglycerides in the form of fatty acids. In stressed condition such as obesity, imbalanced nutrition and drug induced liver injury hepatocytes accumulate excess lipids in the form of LDs whose prolonged storage leads to disease conditions most notably non-alcoholic fatty liver disease (NAFLD). Fatty liver disease has become a major health burden with more than 90% of obese, nearly 70% of overweight and about 25% of normal weight patients being affected. Notably, research in recent years has shown LD as highly dynamic organelles for maintaining lipid homeostasis through fat storage, protein sorting and other molecular events studied in adipocytes and other cells of living organisms. This review focuses on the molecular events of LD forma-

Abbreviations: ACAT, acyl-CoA cholesterol acyltransferase; ACC, acetyl CoA carboxylases; ACLY, ATP citrate lyases; ACSL, acyl CoA synthetases long chain family; ADRP, adipose differentiation related protein; AGP, advanced glycation end products; AGPAT, acylglycerophosphate acyltransferase; AHR, aryl hydrocarbon receptors; ALT, alanine aminotransferases; AMPK, AMP-activated protein kinases; ApoB-100, apolipoprotein B-100; Arfs-COPI, ADP-ribosylation factor1–coat protein complex1; αSNAP, alpha soluble NSF adaptor protein; ASO, anti-sense oligonucleotide; AST, aspartate aminotransferases; ATG, Autophagy related proteins; ATGL, adipose triglyceride lipase; BACS, bile acid acyl-CoA synthetases; BAT, brown adipose tissue; CAP, cleavage activating protein; CB_1, cannabinoid receptor 1; CCL2, chemokine C–C motif ligand 2; CCR2, C–C chemkoine receptor type 2; CD36/FAT, cluster of differentiation 36 /fatty acid translocases; CERP, cholesterol efflux regulatory protein; C/EBP, CAAT/enhancer-binding proteins; CGI-58, comparative gene identification-58; ChREBP, carbohydrate regulatory element binding protein; CIDEC, cell death inducing DNA fragmentation factor A like effector C; CK-18, cytokeratin 18 fragment; CPT, carnitine palmitoyltransferase; CREBH, cAMP responsive element binding protein; CRP, C-reactive protein; CVD, cardiovascular diseases; DAG, diacylglycerol; DGAT, diacylglycerol acyltransferase; DILI, drug induced liver injury; ECM, extracellular matrix; EE, early endosome; eIF2, eukaryotic initiation factor2; ELOVL, elongases; eNOS, endothelial nitric oxide synthetase; ER, endoplasmic reticulum; ERK2, extracellular regulated kinases; FA, fatty acid; FABP, fatty acid binding protein; FA-CoA, fatty acyl-CoA; FADS, fatty acid desaturases; FAF2, FAS-associated factor 2; FAS, fatty acid synthase; FATP, fatty acid transport proteins; FFA, free fatty acid; FGF21, fibroblast growth factor 21; FIT, fat storage inducing transmembrane proteins; FOXA2, fork head box protein A2; FOXO1, fork head box O1; FXR, farnesoid X receptor; γGT, gamma glutamyl transpeptidase; GK, glucokinases; GLUT, glucose transporter; GLUD, glutamate dehydrogenes; GSTα, glutathione S transferase alpha; GPAT, glycerol 3 phosphate acyltransferases; GPLR, G protein linked receptors; HCC, hepatocellular carcinoma; HFD, high fat diet; Hh, hedgehog ligands; HIG2, hypoxia inducible gene 2; HNF4α, hepatocyte nuclear factor 4 alpha; HSC, hepatic stellate cells; HSL, hormone sensitive lipase; HUFA, high unsaturated fatty acid; Ihh, Indian hedgehog; IL-6, interlukin 6; INSIG2, insulin induced gene2; IR, insulin resistance; IRS, insulin receptor substrate; JNK, c-Jun NH2 terminal kinases; KC, kupffer cells; KO, knock-out; LAM, LD associated membrane; LCFA, long chain fatty acids; LD, lipid droplet; LDH, lactate dehydrogenase; LDLR, low density lipoprotein receptors; LFABP, liver fatty acid binding proteins; L-PK, liver pyruvate kinases; LRH1, liver receptor homolog1; LSEC, liver sinusoid endothelial cells; L-TSC, liver tuberous sclerosis protein complex; Ly6C, lymphocyte antigen 6 complex locus c; LXRα, liver X receptor α; MADAG, monoalk(en)yl diacyl glycerols; MAG, monoacyl glycerol; MAPK, mitogen activated protein kinase; MCP1, monocyte chemoattractant protein1; MTP, microsomal triglyceride transfer protein; MF-HSC, myofibroblastic hepatic stellate cells; miRNA, microRNA; mTORC1, mammalian target of rapamycin complex 1; MUFA, mono unsaturated fatty acid; NAFLD, non-alcoholic fatty liver disease; NCEH1, neutral cholesteryl ester hydrolase1; NEFA, non-esterified fatty acid; NF-κB, nuclear factor κB; NK, natural killer; NSF, N-ethylmaleimide-sensitive factor; PAI1, plasminogen activator inhibitor type-1; PA, phosphatidic acid; PAP, phosphatidic acid phosphohydrolase; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PGE2, prostaglandin E2; PI, phosphatidylinositol; PKA, protein kinases A; PKD, protein kinase D; PLD, phospholipase D; PNPLA, patatin-like phospholipase domain-containing protein; PPAR, peroxisome proliferator activated receptor; PPRE, peroxisomal proliferator regulatory element; PEMT, phosphatidyl ethanolamine N-methyl transferase; PS, phosphatidyl serine; PSD, phosphatidyl serine decarboxylase; PUFA, poly unsaturated fatty acid; PXR, pregnane X receptors; Rheb, Ras homologue enriched in brain; ROCK, RhoA associated kinase; ROS, reactive oxygen species; RXR, retinoid X receptor; SC, sub cutaneous; SCAP, SREBP cleavage activating protein; SCD, steroyl CoA desaturases; SE, sterol esters; SEC, sinusoidal endothelial cells; Shh, sonic hedgehog; S6K, S6 kinase; SNAP23, synaptosomal associated protein of 23 kDa; SNARE, soluble N-ethylmaleimide-sensitive factor attachment protein receptor; SOCS, suppressor of cytokine signalling; SPFH, Stomatin Prohibitin Flotillin-HflC/K; SRE, sterol regulatory element; SREBP1c, sterol regulatory element binding protein 1c; STAT, signal tranducer and activator of transcription; T1DM, type 1 diabetes mellitus; T2DM, type2 diabetes mellitus; TG, triglyceride; TIMP1, tissue inhibitor of metalloproteinases; TLR, toll like receptors; TNFα, tumor necrosis factor α; TR, thyroid receptor hormone; TRX, thioredoxin; TZD, thiazolidinediones; UGCG, UDP glucose ceramide glucosyltransferase; UDCA, ursodeoxycholic acid; UFA, unsaturated fatty acids; UPR, unfolded protein responses; USP, ubiquitin specific proteases; VAMP4, vesicular associated protein 4; VDR, vitamin D nuclear receptor; VLDL, very low density lipoprotein; VIM, vimentin; VLACS, very long chain acyl-CoA synthetases; VLDLR, very low density lipoprotein receptor.

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Lipotoxicity
Metabolic syndrome
Cellular cross talks

tion in hepatocytes and the importance of cross talk between different cell types and their signalling in NAFLD as to provide a perspective on molecular mechanisms as well as possibilities for different therapeutic intervention strategies.

Contents

1. Introduction

The liver is the largest solid organ in the body and is primarily comprised of hepatocytes. This organ plays a key role in metabolism, detoxification and protein synthesis. Overnutrition is the most common cause for excess lipid accumulation in hepatocytes and it is estimated that more than six hundred million people worldwide with overweight will develop fatty liver disease [1]. A hallmark of hepatic steatosis is the formation of lipid droplets and a size of 50 nm to 1 μm in diameter is considered to be a temporary excess lipid storage organelle within hepatocytes [2,3]. In recent years much effort has been invested as to improve an understanding of the different aspects of LD formation, the proteins involved and an identification of metabolic pathways that determine the LD formation [2–15]. Thus, extensive knowledge obtained on the biology of LDs in adipocytes is now compared to an evolving understanding of the molecular events leading to LD formation in hepatocytes and includes an assessment of interactions of LDs with other cellular components as well as perturbed metabolic pathways in the onset and progression of fatty liver disease.

Hepatic steatosis, being a multi-factorial disease, has a prevalence of up to 30% in the European population [16]. Non-alcoholic steatohepatitis (NASH) is subsumed in NAFLD where fat accumulation in the liver is associated with inflammation, scarring and ballooning of hepatocytes. NASH is categorised under the two hit model where the first hit is hepatic steatosis which is a milder