

Review

The Role of (Nuclear) Lipid Droplets in the Pathogenesis of Metabolic Syndrome

Natalia Todosenko¹, Kristina Yurova¹, Olga Khaziakhmatova¹, Maria Vulf¹, Vladimir Malashchenko¹, Aleksandra Komar¹, Ivan Kozlov², Igor Khlusov^{1,3}, Larisa Litvinova^{1,3,*}

¹Center for Immunology and Cellular Biotechnology, Immanuel Kant Baltic Federal University, 236016 Kaliningrad, Russia

²Department of Organization and Management in the Sphere of Circulation of Medicines, Institute of Postgraduate Education, I.M. Sechenov Federal State Autonomous Educational University of Higher Education-First Moscow State Medical University of the Ministry of Health of the Russian Federation, 119991 Moscow, Russia

³Laboratory of Cellular and Microfluidic Technologies, Siberian State Medical University, 634050 Tomsk, Russia

*Correspondence: larisalitvinova@yandex.ru (Larisa Litvinova)

Academic Editor: Graham Pawelec

Submitted: 26 September 2024 Revised: 26 November 2024 Accepted: 27 December 2024 Published: 17 June 2025

Abstract

Metabolic syndrome (MetS) is a widespread multi-component pathological condition characterized by meta-inflammation and cellular dysfunction. MetS and other metabolic diseases (metabolic dysfunction-associated steatotic liver disease (MASLD), cardiovascular-kidney-metabolic syndrome (CKMS)) stem from the disorder of energy metabolism and changes in the structure and function of specialized organelles such as lipid droplets, endoplasmic reticula, mitochondria, and nuclei. The discovery of lipid droplets within the nucleus and the investigation of their functions across various cell types in both health and disease provide a foundation for discussing their role in the development and progression of metabolic syndrome. This review examines studies on lipid droplets in the nucleus, focusing on pathways of formation, structure, and function. The importance of (nuclear) lipid droplets in liver and brain is emphasized in the context of inflammation associated with obesity, MetS, and liver disease. This suggests that these structures are promising targets for the development of effective drugs against diseases associated with dysregulation of energy metabolism.

Keywords: metabolic syndrome; obesity; nuclear lipid droplets; non-alcoholic fatty liver disease; hypothalamic inflammation

1. Introduction

Metabolic syndrome (MetS) is a widespread pathological condition encompassing obesity, insulin resistance (IR), dyslipidemia, triglyceridemia, and similar disorders. In MetS, morphological and functional changes occur at the organ and tissue level (adipose tissue, bone marrow, liver), at the cellular level (adipocytes, neurons, hepatocytes, monocytes, stellate cells, macrophages, lymphocytes) and at the subcellular level (nucleus, endoplasmic reticulum (ER), mitochondria), leading to meta-inflammation, and the development of cardiovascular diseases, liver cirrhosis, cancer, and other serious conditions [1–7]. The significance of this connection prompted a 2020 proposal to define diagnostic criteria and rename non-alcoholic fatty liver disease (NAFLD), a chronic liver condition, as metabolic-associated fatty liver disease (MAFLD) to emphasize its relationship with MetS [8]. In addition, MAFLD is closely associated with obesity and the development of chronic kidney disease (CKD), the latter characterized by a gradual loss of normal kidney function due to excessive accumulation of lipid droplets (LDs) and oxidative damage [9]. The combination of the above pathologies constitutes cardiovascular-kidney-metabolic syndrome (CKMS), a systemic multiorgan disease resulting from adipose tissue dysfunction and leading to arterial, cardiac and renal damage [10].

The study of the molecular structure of intracellular organelles, their interactions, and the proteins involved in maintaining cell homeostasis and responding to changes in energy balance is a critical medical and biological endeavor. It enables the identification of potentially effective targets for controlling and preventing serious diseases [6]. A close relationship between the development of metabolic disorders (obesity, MetS, MAFLD, metabolic dysfunction-associated steatotic liver disease (MASLD), CKD, CKMS) and oncological diseases of various origins has been frequently highlighted in the literature [11–17]. On the one hand, the incidence of clear cell renal cell carcinoma increases in obese individuals. On the other, the course of clear cell renal cell carcinoma in obese patients has a more favorable prognosis than in patients with a normal body mass index (BMI) [18]. This pathological interdependence is based on a disorder of adipose tissue function/distribution [1] associated with genetic/epigenetic factors and low-grade chronic inflammation that affects nearly all tissues and organs [19].

Moreover, epigenetic and genetic mechanisms are of paramount importance for the regulation of metabolism/neuronal activation in the nuclei and structures of the brain regulating appetite phases, taste preferences, and food intake the pituitary, the hypothalamus, and the



pons [19]. A high-calorie diet initially activates adaptive mechanisms that alter cellular metabolism, hormone production, and inflammatory mediator synthesis. These changes drive target cell and organ responses, ultimately establishing a persistent inflammatory state against the background of altered homeostasis of the body. In obesity, epigenetic changes in proteins and transcription factors lead to reprogramming of cellular homeostasis, resulting in disruption of cells and tissues in the periphery [19].

Furthermore, morphofunctional changes and an inflammatory response are observed in obesity in the key area of the brain responsible for homeostasis and glucose metabolism the hypothalamus [20,21]. Metabolic regulators in the hypothalamus include the agouti-related protein (AgRP) and the proopiomelanocortin (POMC) neurons in the arcuate nucleus (ARC), both altering neuronal activity [22]. Disruption of the regulatory mechanism increases food intake and energy expenditure due to chronic inflammation in the hypothalamus [23]. This inflammation is characterized by the activation of resident microglia, macrophage infiltration [24], and impaired pericyte function [25] in the context of obesity and high-fat diet (HFD) intake [26,27].

Metabolic and nutrient distribution pathways in the neurons of the mediobasal hypothalamus (MBH) play a critical role in the development of metabolic disorders caused by changes in the levels of hormones, such as leptin, insulin, ghrelin, and glucose. Malonyl-CoA levels are also tightly regulated by glucose via the AMP-activated protein kinase (AMPK) pathway in MBH [28]. Glucose-mediated AMPK inhibition reduces the oxidation of fatty acid (FA) and increases the esterification of FA to triacylglycerol (TAG) in hypothalamic neurons and astrocytes [29]. It also leads to the activation of acetyl-CoA carboxylase (ACC) and the formation of malonyl-CoA, which is derived from glucose. Malonyl-CoA reduces mitochondrial acyl-CoA oxidation by inhibiting carnitine palmitoyltransferase-1 (CPT-1). While malonyl-CoA is a substrate for the synthesis of fatty acids by fatty acid synthases, glycerol-3-phosphate obtained from glycolysis provides the basis for TAG formation. Thus, glucose metabolism reduces the oxidation of fatty acids and promotes the storage of glucose-derived carbon in the form of lipids [22].

Mechanistically, hypertrophy/hyperplasia of fat cells in patients with obesity leads to tissue hypoxia of parenchymatous organs, which impairs the oxidation of fatty acids in the mitochondria of target cells with their subsequent accumulation, coupled with the development of fatty degeneration, further hypertrophy of adipose tissue, and damage to organs and systems, including the liver, cardiovascular system, brain, and kidneys. Impaired cell function is often accompanied by mitochondrial dysfunction, high reactive oxygen species (ROS) production, lipid raft dysfunction, ER damage, nuclear membrane damage, lipid droplet formation, and, finally, the inability of the cell to compensate for lipotoxicity and maintain viability under stress by

secreting alarmins and triggering apoptosis [6]. MetS, obesity, MASLD, and CKMS are associated with changes in lipid homeostasis in cells against the background of LDs formation. They regulate both cellular energy reserves and physiological processes by controlling signaling, autophagy, and posttranslational modifications in health and disease [30–32]. Recently discovered LDs within the nucleus under stress conditions highlight their direct role in regulating gene expression [33]. A detailed understanding of the functional potential of LDs in different locations in the development of metabolic diseases and in health will help identify targets (proteins, components of signaling pathways) whose manipulation could reduce the risk of complications and break the “vicious cycles” by blocking the key link in the pathogenesis of MetS and obesity.

The aim of this review is to consider the structural and functional potential of LDs of different localizations with emphasis on nuclear LDs, as well as to describe of the possible role of LDs in metabolic diseases, such as MetS, obesity, and MASLD, from the perspective of molecular mechanisms responsible for the regulation of cellular energy metabolism under conditions of excessive nutrient intake and impaired utilization (Fig. 1).

2. Types of Lipid Droplets, Their Structure, and Properties

LDs, also called liposomes and oil bodies (adiposomes), are unique organelles ranging from 1 to 100 μm in size and specialized in the storage (buffering) of intracellular lipids in the cytoplasm (cytoplasmic lipid droplets (cLDs)). LDs consist of a phosphatide monolayer membrane (phosphatidylcholine, phosphatidylinositol) with outward-facing polar groups and acyl chains interacting with a hydrophobic core consisting of neutral lipids (triglyceride (TG), sterol/cholesterol ester) and non-polar lipids (diacylglycerol, cholesterol, monoacylglycerol) [34].

The heterogeneity of LDs in terms of size and composition has been repeatedly observed across various cell types. The largest LDs were associated with white adipocytes up to 100 μm ; in brown adipocytes, the diameter of LDs measured 10 μm in adipocyte cells and 1–4 μm in non-adipocyte cells. These differences may also be attributed to the ability of LDs to retain hydrophobic antibiotic molecules, thereby regulating the viral life cycle [35].

Under normal conditions, LDs are located in the cytoplasm; however, certain cells contain unique structures localized in the nucleus, known as nuclear LDs (nLDs), which suggest novel functional roles for LDs in cell biology [33]. nLDs are found in hepatocytes, differentiated adipocytes, fibroblasts (though rarely), intestinal epithelial cells (Caco2), osteosarcoma cells (U2OS), human and rat hepatocarcinoma cells, cell lines (HepG2, McA-RH777, Huh7), yeast, and *Caenorhabditis elegans* cells [36–38].

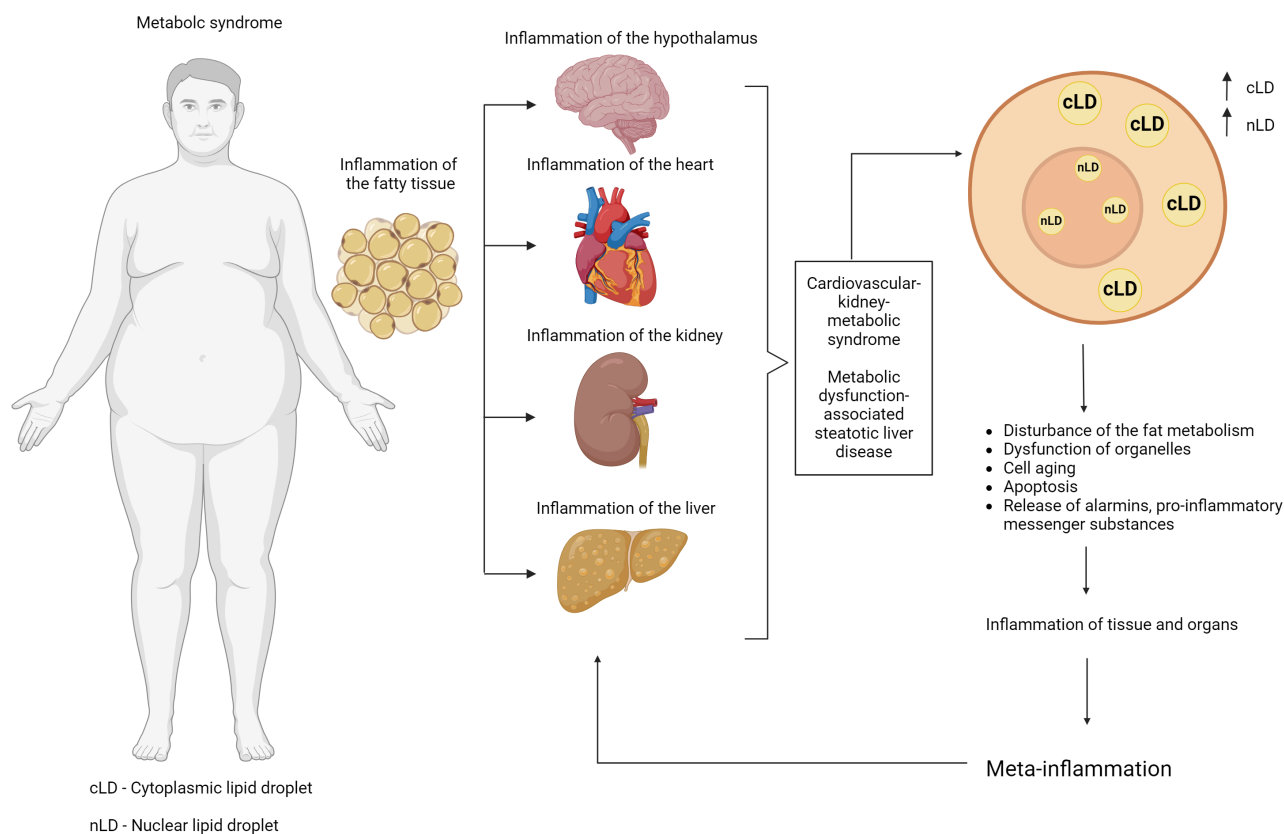


Fig. 1. Possible linking role of lipid droplets in the progression of metabolic syndrome (and its components) and the development of pathological meta-inflammation. Created with [Biorender.com](https://www.biorender.com).

2.1 Formation of Lipid Droplets in the Endoplasmic Reticulum

According to the classical model, the ER is the site of formation (nucleation), growth, and budding of nLDs. At the same time, ER proteins are able to regulate the budding of LDs into the cytoplasm or to induce their translocation into the nucleus.

In the ER, neutral lipids are synthesized by the enzymes acyl-CoA:diacylglycerol acyltransferase (DGAT)1/DGAT2, while sterol esters are synthesized by the enzymes acyl-CoA:cholesterol O-acyltransferase (ACAT)1/ACAT2 [35,39].

TAG synthesis. De novo synthesis of TAG and LDs in the ER [40–43] is catalyzed by four sequential enzymes: glycerol phosphate acyltransferase (GPAT), acyl glycerol phosphate acyltransferase (AGPAT), phosphatidic acid phosphohydrolase (PAP), and acyl-CoA:diacylglycerol acyltransferase (DGAT) [44]. The final step of TAG synthesis is catalyzed by DGAT enzymes that covalently bind fatty acyl-CoAs (FA-CoAs) to diacylglycerols (DAGs). In mammals, the two enzymes DGAT1 (ER) and DGAT2 (ER, LDs) compensate each other in TAG storage [45–47]. In the ER, DGAT1 regulates the detoxification of excess lipids [46,48].

Synthesis of steryl esters (SE). Enzymes for the biosynthesis of SE, which are localized in the ER and

LDs [39], regulate the TAG:SE ratio depending on growth conditions and cell type [49]. The formation of the lipid core of LDs in the ER follows fundamental principles of physical chemistry [50–52]. Neutral lipids (TAG, SE) are formed by esterification of activated fatty acids to diacylglycerol/sterol (cholesterol) by ER enzymes. Sterol esters are formed by acyl-CoA:cholesterol O-acyltransferases (ACAT1, ACAT2). At low concentrations, neutral lipids are scattered between the leaflets of the ER bilayer, while at TAG concentrations of 5–10 mol% [53], they fuse into an oil lens through a delamination process, thus minimizing the interfacial tension/energy cost associated with deleterious effects between the two immiscible phases (neutral lipids and phospholipid bilayers) [54]. Subsequently, a portion of the newly formed LDs (initial LDs (iLDs)) recruits ADP-ribosylation factor 1 (Arf1)/coat protein complex I (COP-I) enzymes and proteins across the ER-LDs membrane bridges to facilitate local TG synthesis, forming larger expanding (luminal) LDs (eLDs) [41,55,56]. The phospholipid composition of the ER membrane plays a crucial role in LD budding, as it influences the surface tension of the membranes [57,58]. The tension is important to maintain the round shape of LDs, while the phospholipid composition influences the efficiency of budding due to geometric effects [50].

The surface tension facing the ER lumen is higher than that facing the cytoplasmic membrane [55], and budding of LDs tends to occur when the tension is lower [56]. However, changes in the local composition of ER phospholipids play a pivotal role in this process [56,57].

Lipids with inverted shape (predominantly hydrophilic head) phosphatidylinositol (PI) and lysophospholipids generate a positive curvature that facilitates the formation/detachment of LDs towards the cytosol [40,58,59]. Cone-shaped lipids (predominantly lipolytic structures), such as diacylglycerol (DAG) and phosphatidylethanolamine, induce negative curvature that promotes incorporation of LDs into the ER membrane bilayer [58,60] and prevents budding by stabilizing the association between the ER and LDs [40,50,61].

The manner in which ER architecture influences lipid membrane composition and LD formation remains unexplored. The ER consists of flat membrane sheets and curved tubes supported by curvature-supporting and stabilizing proteins reticulons and atlastins [62]. However, ER-associated proteins (class I proteins), such as fat storage-inducing transmembrane protein (FITM), seipin, lipid droplet assembly factor 1 (LDAF1), and dynamin-related protein 1 (DRP1), are also involved in LD biogenesis.

SEIPIN. Seipin coordinates LD biogenesis by forming a complex with an oligomeric toroidal structure, which traps neutral lipids (TAG, DAG) in the ER bilayer and promotes LD nucleation [63–65].

FITM. These conserved transmembrane proteins of the ER bind TG and DAG, promote lipid accumulation (in the case of FITM), and play a role in LD formation [66]. The diphosphatase activity of FITM supports LD formation and nucleation and protects against cellular stress [67]; FITM is required to stimulate the formation of LDs from the ER.

FITM2 is the only fatty acyl-CoA diphosphatase in the ER lumen. Binding of phosphoanhydride upon cleavage of acyl-CoA is thought to be linked to conformational changes that drive active pumping of neutral lipids across the membrane, reducing DAG content near the LD budding site at the ER [67]. FITM2 has been found to be involved in the metabolism and distribution of non-layer lipids, affecting LD biogenesis along with the curvature and surface tension of the ER monolayer [68]. Moreover, FITM2 has been shown to localize to sites where LDs form and promote LD appearance by reducing DAG levels [67]. It also binds to the cytoskeletal protein Septin 7, which ensures normal LD biogenesis, and to proteins that form ER tubules (reticulon-4 (Rtn4), receptor expression enhancing protein 5 (REEP5)) [69]. FITM2 and Septin 7 interact during differentiation of adipocytes at LD nucleation sites [69].

In addition, depletion of ER-associated proteins SCS3/YFT2 delays the formation of LDs and their retention in the ER [67].

Thus, the functional capacity of FITM2 is mediated by TG biogenesis and the redistribution of TG into LDs, which influences the surface tension of LDs and determines the direction of budding/movement of LDs, toward the cytoplasm or ER.

LDAF1 (TMEM159). The seipin-binding protein LDAF1 (TMEM159)/promethin is an interaction partner of seipin. Together, LDAF1 and seipin form an oligomeric complex (600 kDa) that is decimated by TG. LDAF1 recruits seipin and marks the sites of LD formation and regulates LD biogenesis through the accumulation and distribution of TG in LDs [70]. During LD maturation, LDAF1 dissociates from seipin and migrates to the surface of LDs [71].

In the absence of LDAF1, LDs can only be formed in the ER at high TG concentrations [71].

DRP1. The dynamin protein DRP1 is involved in the division of mitochondrial membranes [72], with DRP1 oligomers localized in the ER. DRP1 has been found to form peripheral ER tubules that establish contact with mitochondria [73]. In adipocytes, β -adrenergic activation of protein kinase A (PKA) stimulates the phosphorylation and translocation of DRP1 into the ER [72], which promotes the exit of mature LDs from the ER into the cytoplasm.

DRP1 deficiency in adipose tissue is associated with retention of LDs in the ER lumen and processes such as ER stress, abnormal autophagy, morphological changes of cLDs, and mitochondrial dysfunction. This deficiency causes impaired energy expenditure throughout the body, as observed in Adipo-Drp flx/flx mice [72]. In addition, dominant-negative mutations of DRP1 pathologically alter the structure of the ER membrane and impair the dissociation of LDs from the ER [72].

2.2 Nuclear Lipid Droplets

The nucleus is separated from the cytoplasm by a two-layered phospholipid nuclear membrane consisting of the outer (ONM) and the inner nuclear membrane (INM). The luminal space between the membranes merges into the ER lumen. The invaginations of the nuclear membrane into the lumen of the nucleoplasm form the nucleoplasmic reticulum (NR) of two types. An extension of the INM, type-I NR can interact with the nucleoplasm, while type-II NR consists of invaginations of both the inner and outer nuclear membranes [74].

Nuclear lipids, which are actively involved in cell proliferation, differentiation and apoptosis, are important structural and functional components of the nucleus. Lipids make up 16% of the nuclear content, followed by the most important components proteins and nucleic acids [75].

The activity of excess FA promotes the formation of nLDs, which consist of a neutral lipid core and lipid biosynthesis enzymes. Similar to cLDs, surface tension and the composition of lipids with either negative or positive intrinsic curvature play a critical role in the biogenesis of nLDs [59]. The classical site for the synthesis of LDs is

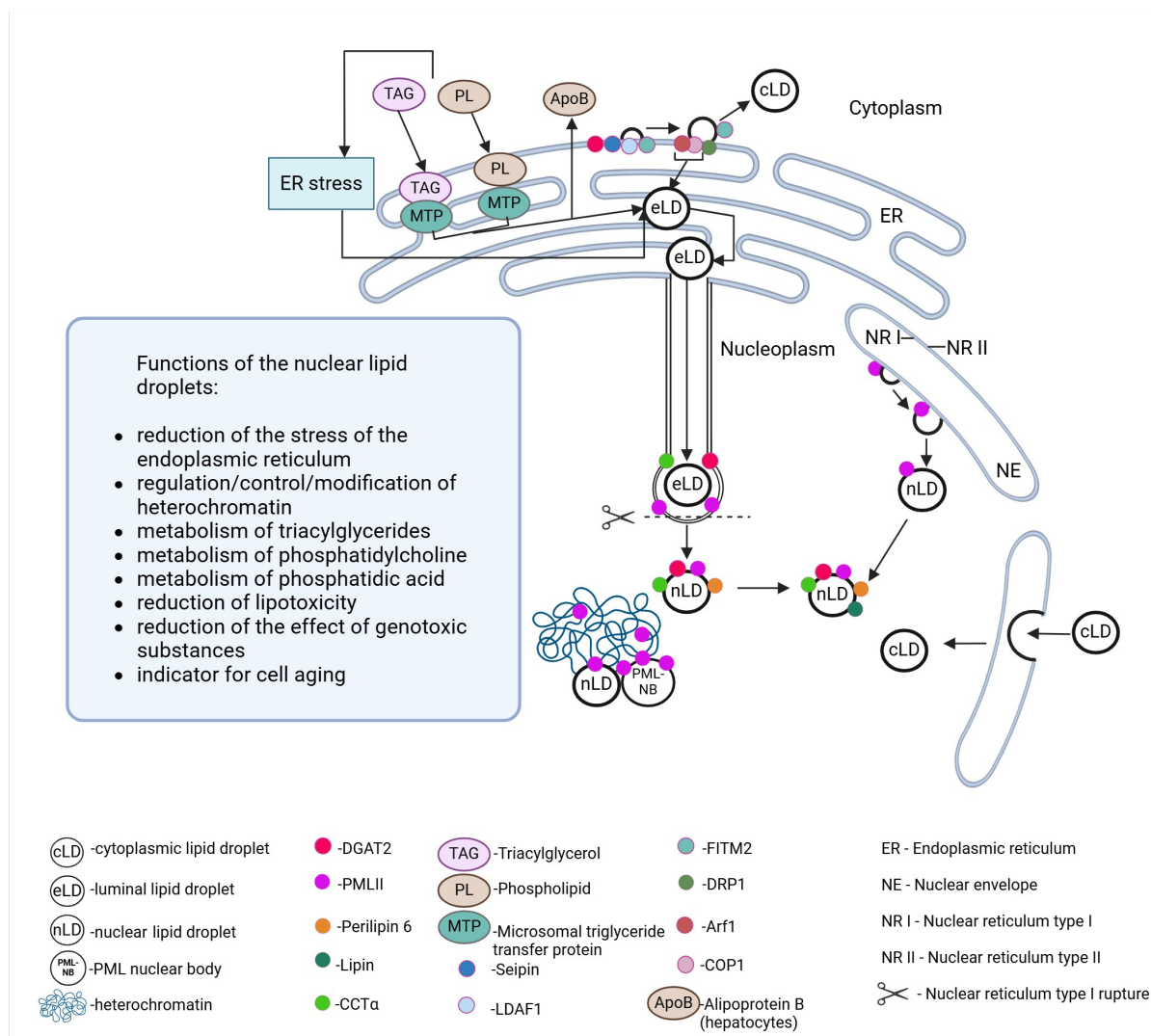


Fig. 2. Formation of intra-/extranuclear nuclear lipid droplets and their functional potential within the nucleus. Created with Biorender.com.

the ER, which is directly connected to the nuclear envelope. Another important factor is the INM, which has its own lipid metabolism facilitated by proteins and enzymes that regulate the transfer of DAG and TG [76]. In general, the process of nLD formation from the ER is controversial and challenging to define in terms of its molecular components. A variety of pathways for the formation of nLDs have been described in the literature to date: (1) from lipoprotein precursors in the ER lumen (hepatocytes, lipoprotein-producing cells) with subsequent translocation to the nucleus and (2) with subsequent translocation to the INM [33]. Both mechanisms of nLD formation may occur in the same cell and are likely interconnected. cLDs have also been described as capable of entering the nucleus [36]. Moreover, it has been hypothesized that a specific timing governs the budding of maturing LDs (eLDs) into the cytoplasm or their movement toward the nucleoplasm along type-I NR, leading to the subsequent formation of nLDs [77]. All these mechanisms are directly related to proteins and enzymes localized in the ER, INM, and LDs (Fig. 2).

Although the functional capacity of nLDs is not well understood, experimental modeling has uncovered some of their key properties. They may serve as platforms for activating CTP:phosphocholine cytidyltransferase α (CCT α), the rate-limiting enzyme of phosphatidylcholine synthesis [78], and the modulation of the molecular components of promyelocytic leukemia nuclear bodies (PML NB) [33]. The induction of nLD formation is associated with replicative senescence and cellular stress [79], suggesting interactions between DNA and nLDs [77]. The connection between nLDs and PML NB also suggests that they serve as sites for regulating the expression of specific genes, particularly those involved in lipid metabolism and cellular energy homeostasis [36,80] (Fig. 2).

2.2.1 Formation of Nuclear Lipid Droplets from Endoplasmic Reticulum

The earliest identified mechanism of nLD biogenesis involves the migration of mature eLDs (expanding LDs) into the nucleoplasm. Although this nLD formation mech-

anism follows the classical pathway of LD development by budding into the cytoplasm, at a certain stage and under the influence of inducing conditions, it starts to work towards the nucleus.

In the ER of hepatocytes (and hepatoma cells), TAG-enriched apolipoprotein B100 (apoB)-containing very low-density lipoproteins (VLDLs) accumulate and migrate via COPII transport vesicles toward the cis Golgi to be subsequently secreted into the blood. In the ER lumen, microsomal triglyceride transfer protein (MTP) facilitates the delivery of TAG and phospholipids to apoB to form VLDL precursors and eLDs. ER stress and TAG overproduction induce the translocation of a portion of eLDs from the ER to the INM extension (type-I NR) via colocalized enzymes of TG synthesis (DGAT2) and phosphatidylcholine (CCT α). This is followed by disruption of type-I NR at sites containing the PML-II protein [78] but deficient in lamin A, lamin B receptor (LBR), and SUN1/2 proteins. In the nucleoplasm, nLDs expand and mature by recruiting the DGAT2 and CCT α enzymes to increase TAG and phosphatidylcholine synthesis [36].

2.2.2 Formation of Nuclear Lipid Droplets from the Inner Nuclear Membrane

Another mechanism for the formation of nLDs (yeast, U2OS) involves the promyelocytic leukemia protein (PML) [37] and INM enzymes (GPAT3,4; AGPAT1, lipin-1, DGAT1,2) [81,82]. nLDs formed de novo on the INM contain TAG, DAG, and phosphatidic acid (PA) [81] (Fig. 2).

In yeast, nLDs detach from the INM [76], while their lipid monolayer remains adjacent to the INM [76]. Localized on the INM, seipin is, in turn, necessary for the correct formation of the membrane bridge connecting the INM and nLDs. Phosphatidic acid is converted either to diacylglycerol by phosphatidic acid phosphohydrolase 1 (Pah1) for triacylglycerol synthesis or to cytidine diphosphate diacylglycerol by phosphatidate cytidyltransferase (Cds1) for phospholipid synthesis. Pah1 and Cds1 are present in the INM, and the inhibition of Cds1 promotes nLDs biogenesis. The presence of additional genes involved in lipid synthesis, such as diacylglycerol acyltransferase gene (*Dgal1*) and *Lro1*, in the INM remains unidentified [50,76].

A close association between nLDs and PML protein has been demonstrated in eukaryotic cells. A probable interaction of nLDs with PML-containing nuclear bodies (PML-NB) has also been described, as nLDs carrying the PMLI isoform are characterized by a radial bristle-like structure, a feature typical of PML-NB [37]. The highest colocalization with nLDs of all PML protein isoforms (I-VII) has been found for the PML-II isoform. This is likely due to the specific structure of PML-II, which includes a unique C-terminal domain containing two motifs: one for binding to the nuclear periphery and another for extranuclear localization. The first motif mediates the distribution of the PML-II protein along the nucleoplasmic surface of the INM with the formation of PML-II plaques/patches

(in U2OS cells, cells from the liver). These regions are characterized by the absence of LBR, SUN1 (an integral INM protein) [83] and INM transmembrane proteins associated with lamin A/B. The binding of nLDs to chromatin via membrane-associated PML-II (as in PML-NB) has been implicated, particularly in cells with PML-II plaques/spots [37]. PML-II has been found to play a key role in the formation of 50% of nLDs in Huh7 cells [37]. Silencing of the *PML* gene in U2OS cells has been accompanied by a decrease in the number of nLDs [81], as well as in Huh7 cells, confirming the role of PML-II in binding nLDs to membranes [37] (Fig. 2).

nLDs in hepatocytes are associated with PML NB, which is involved in the regulation of gene transcription [37]. In contrast to perilipin-2 (PLIN2), in mammals, PLIN5 is located in the nucleus and functions as part of a transcriptional regulatory complex that controls mitochondrial gene programs [84]. Although no association of PLIN5 with nLDs is known [50], nLDs have been identified with dyes specific for perilipin-3 (PLIN3) and Rab18 [37]. LDL synthesis in hepatocytes has been found to involve MTP, which is localized in the ER. MTP assists in the transfer of ceramides and sphingomyelin to apoB-containing lipoproteins and participates in the biosynthesis of cholesterol ester and cluster of differentiation 1d (CD1d) [85]. MTP induces the formation of apoB-containing primary particles and ApoB-deficient eLDs in the ER, leading to the production of mature LDL [85–87]. ER stress increases MTP activity [88], induces the accumulation of apoB-deficient LDs, and generates more nLDs, which serve as LDL precursors in the ER lumen. eLDs growing in type I NRs are translocated to the nucleoplasm as the NR membrane ruptures in the presence of localized lamin deficiency and the membrane becomes mechanically unstable. It is assumed that MTP-dependent lipid transfer into eLDs leads to their growth and the destruction of the type-I NR membrane. In addition, the lack of lamins could be related to the presence of the PML-II protein [37,89].

Thus, apoB-deficient eLDs give rise to nLDs [90], which, in turn, recruit CTP:phosphocholine cytidyltransferase α (CCT α), the rate-limiting enzyme in the Kennedy pathway, to synthesize phosphatidylcholine (PC) and enhance de novo PC synthesis [91]. PLIN3 competes with CCT α for binding to LDs in the nucleoplasm. Suppression of PLIN3 enhances PC synthesis by increasing the nucleoplasmic association of CCT α with LDs, while the overexpression of PLIN3 reduces the association of CCT α with nLDs, suppressing PC synthesis [78]. INM-driven lipid accumulation promotes nLDs synthesis via seipin-dependent membrane bridges, genetic circuitry for nLDs synthesis, and nuclear ER crosstalk via sequestration of transcription factors [76,82,92]. Within the lipid nucleosome, lipids interact directly with chromatin via contact sites, affect chromatin structure and condensed regions, and alter gene expression and cell phenotype [93,94]. nLDs are important for the formation, transformation, storage, and function of

lipids in nuclei; they also contribute to the formation of the INM and the maintenance of nuclear homeostasis and the microenvironment. nLDs can provide lipids for nuclear envelope expansion, serving as a platform for the regulation of gene expression by scaffold transcription factors, as observed in yeast (regulation of the transcription factor *Opi1*, which is involved in lipid metabolism) [50,76]. Additionally, nLDs regulate PC synthesis in a competitive manner, dependent on *PLIN3* expression, and activate it during ER stress in hepatocytes [78]. nLDs separate the nucleus from other organelles to segregate nuclear energy and function, although the molecular mechanisms of nLD formation and development vary across cell types [76,82]. Several factors are involved in nLD synthesis and lipolysis, including lipoprotein precursors, enzymes of TG synthesis, mTOR signaling, lipin-1, seipin, FA-binding proteins, and choline kinase α .

Although nLDs are associated with many metabolic disorders, the exact role of nLDs in pathogenesis and pathophysiologic processes remains unclear [93]. In particular, nLDs have been identified in hepatocytes associated with steatosis and chronic hepatitis A1-F1. An analysis of 583 hepatocytes revealed 402 cells with isolated cLDs and 64 cells with LDs localized in the nucleus. Of these cells, 60 exhibited deformed nuclei due to the presence of large cLDs or as a result of the cLDs being partially enclosed by the nuclear membrane within the nucleus, while 4 cells contained true nLDs [95]. However, further research into nLDs is of great interest as there are multiple pathways for nLD formation, and nLDs are likely to have different functions depending on conditions of formation, cell types and degree of cellular stress. A more detailed study of the biology and functioning of nLDs will enhance our understanding of their potential for combating severe metabolic disorders.

3. The Role of Lipid Droplets in the Pathogenesis of Metabolic Syndrome (Obesity, Hypothalamic Inflammation, MASLD, CKMS)

3.1 Complex Mechanism of Interaction Between Metabolic Diseases in which Lipid Droplets May Be the Key Regulator

MASLD denotes a spectrum of histological changes in the liver closely linked to type 2 diabetes mellitus (T2DM) and obesity, sharing similar pathophysiological features with hepatic steatosis, metabolic dysfunction-associated steatohepatitis (MASH), fibrosis, cirrhosis and MASLD-related hepatocellular carcinoma (MASLD-HCC) [96,97]. MASLD is characterized by inflammation, intestinal dysbiosis, and metabolic dysregulation [98,99]. Research indicates a link between MASLD and the development of cardiovascular disease and chronic kidney disease [100–105], contributing to the concept of CKMS. CKMS is characterized by increased concentrations of phospholipid derivatives (ceramides, sphingosine), oxidized LDL, and

lipoproteins (a, b), which are detrimental to renal and cardiac function [106]. All pathological changes in the organs in MASLD and CKMS, related to organelle dysfunction, are also linked to impaired cellular metabolism, oxidative stress, and impaired function and structure of organelles against the background of excessive LD accumulation [107].

3.1.1 Sex-Specific Differences in the Development of Metabolic Diseases

3.1.1.1 Lipid Droplets and Genetic Factors. Genetic factors play an important role in the pathogenesis of MASLD and CKMS [8,96,108].

Genetic alterations include single nucleotide polymorphisms in the following genes: patatin-like phospholipase domain-containing protein 3 (*PNPLA3*), transmembrane 6 superfamily member 2 (*TM6SF2*), membrane-associated O-acyltransferase domain containing 7 (*MBOAT7*), glucokinase regulatory protein (*GCKR*), and hydroxysteroid 17-beta-dehydrogenase 13 (*HSD17B13*) [96].

PNPLA3. The *PNPLA3* gene encodes a multifunctional enzyme involved in liver lipid regulation through its triglyceride lipase and acylglycerol O-acyltransferase activities on the surface of LDs [109]. The strongest risk factor for MASLD is a non-synonymous variant (rs738409 [G]) in the *PNPLA3* gene, which is strongly associated with high liver fat, inflammation, and MASLD-HCC [110]. This mutation codes for a replacement of isoleucine by methionine at position 148 (*PNPLA3-I148M*) [97]. It has been suggested that *PNPLA3-I148M* impairs TAG hydrolysis on cLDs, causing steatosis [111,112]. Expression of *PNPLA3-I148M* in stellate liver cells has been found to lead to mitochondrial dysfunction due to the accumulation of free cholesterol (impaired Peroxisome proliferator-activated receptor gamma (*PPAR* γ), liver X receptor (*LXR*) signaling and the stimulation of Hedgehog and yes-associated protein (*Yap*) signaling pathways), as well as to the activation of fibrotic processes [113,114] through impaired hydrolysis of retinyl esters and reduced release of retinol [112]. A localization of *PNPLA3-I148M* in the Golgi apparatus and the central point of LDs formation the ER [97,115] has been found. At the same time, *PNPLA3-I148M* is highly expressed in renal podocytes, contributing to renal dysfunction [116–119]. *PNPLA3-I148M* is thought to impair the physiological functions of *PNPLA3* and lead to reduced release of retinol from LD, which may lead to renal dysfunction in the kidneys [120], while *PNPLA3-I148M* can directly alter the composition of LDs in the kidneys, leading to renal and CKD dysfunction [120]. Moreover, the deposition of LDs associated with *PNPLA3-I148M* may result in their nuclear compression, contributing to cellular dysfunction and ROS production, which in turn induces renal dysfunction [120]. A positive association of *PNPLA3-I148M* with premature coronary heart disease (CHD) has also been found in patients with T2DM [121]. *PNPLA3* inhibition increases the risk of severe cardiovascular disease, including

coronary atherosclerosis, coronary artery disease, and myocardial infarction [122].

TM6SF2. Predominantly expressed in the liver and small intestine, the *TM6SF2* gene codes for proteins involved in lipid metabolism through TAG secretion in the liver [123]. The variant *rs5842926* (C>T) accounts for lower total cholesterol and LDL levels [124], while increasing the risk of liver fibrosis and MASLD-HCC [125]. Although *TM6SF2* E167K may have a protective effect on the development of coronary heart disease, it elevates the risk of developing hepatic steatosis [126–128]. *TM6SF2 rs5854292* has been associated with CKD in patients with MAFLD [129,130]. The *TM6SF2* gene has been shown to have a protective role in the development of cardiovascular pathologies in MASLD [100].

MBOAT7. The *MBOAT7* gene encodes an integral membrane protein that serves as a lysophosphatidylinositol acyltransferase for the transfer of polyunsaturated acyl-CoA to lysophosphatidylinositol and other lysophospholipids in the Lands cycle. The variant *rs641738* (C>T) is associated with MASLD and leads to severe liver damage [131], severe MAFLD, susceptibility to MASH and HCC, and abnormal alanine aminotransferase (ALT) levels in children [101]. An association has been found between the *MBOAT7* gene and cardiometabolic diseases [132], including venous thromboembolism [99], as well as between the *MBOAT7* polymorphism and CKD in patients with liver disease [129].

GCKR. The *GCKR* gene encodes a glucokinase regulatory protein that inhibits glucokinase expressed in the liver and pancreatic islet β -cells. *GCKR* variants are associated with TG, IR, and plasma glucose levels [133]. Two common variants in the *GCKR* gene, *rs780094* (C>T) and *rs1260326* (C>T), affect liver fat content, TG, and lipoprotein levels, and are linked to more advanced stages of fibrosis and MASH [133]. The *rs1260326* variant is associated with the development of cardiometabolic disorders [134]. A connection between the T/T genotype of the *GCKR rs1260326* polymorphism and an increased risk of developing CKD is tentatively suggested [135]. *GCKR* variants are associated with the development of T2DM and dyslipidemia [133]. *GCKR* expression has been shown to be associated with a low risk of developing MASLD [133].

MLXIPL. The single nucleotide polymorphism *rs3812316* has been linked to α -linolenic acid uptake, serum TG and apoB levels [133].

ZPR1. *rs964184* polymorphism of the *ZPR1* gene is associated with lipid and metabolic disorders, including cardiovascular disease, liver disease, and T2DM, serving as a potential biomarker for MASLD in GWA studies [133].

HSD17B13. *HSD17B13* encodes LDs enzymes required for the degradation of LDs in the liver [136]. The *rs72613567* (T>TA) variant has been shown to protect against MASLD in the context of *PNPLA3*-I148M polymorphism and attenuate liver damage by reducing *PNPLA3* mRNA expression [137,138]. The *HSD17B13* gene

is particularly involved in retinol metabolism, inactivating hepatic stellate cells and protecting kidney function [136]. *HSD17B13* is expressed in the kidneys, ureter, and bladder, contributing to the accumulation of lipids in CKD [139]. A closer examination of the genetic components of MASLD and CKMS and their possible association with LD formation and dysfunction will help identify individuals at high risk of developing these pathologies. Complementing the molecular aspect of the pathogenesis of metabolic diseases (MASLD and CKMS) with genetic information may lead to a more accurate prediction of disease progression and effective treatment.

It is necessary, however, to take into account the genetic background and chromosomal alterations affecting individual predisposition to the development of liver metabolic diseases. For example, the aforementioned *PNPLA3*-I148M variant on chromosome 22 causes an increased risk of MASLD and occurs predominantly in women [140–142]. Conversely, the RNA-binding motif gene on the Y chromosome and the testicular-specific protein Y coordinator (*RBMY*), which regulates the activity of androgen receptors, contribute to the development of HCC in men [143]. Women have a higher methylation profile in the X chromosome compared to men, which leads to a change in gene expression in the liver and lowers cholesterol and TG levels in accordance with the metabolic activity regulating the development of hepatopathologies [144].

Thus, there are undeniable sex differences that determine the frequency and differential risk of developing metabolic diseases in men and women.

3.1.1.2 Lipid Droplets and Hormones. Sexual dimorphism plays a crucial role in the development of MASLD and CKMS, as estrogens and androgens affect the risk of liver and metabolic diseases [140]. Estrogens regulate functions related to sexual differentiation, reproduction, bone health, and control of the main nucleus of energy metabolism, with effects influenced by sex, age, and diet [145]. In addition, estrogens operate by facilitating insulin secretion and controlling the availability of glucose. They also modulate energy distribution by favoring the use of lipids as the main energy substrate when their availability exceeds that of carbohydrates. Moreover, estrogens activate antioxidant mechanisms, controlling the energy metabolism of the whole body [145].

Estrogen has a tissue-specific effect. For instance, adipose differentiation-related protein (ADRP), a major component of LDs closely associated with the onset of lipid accumulation, has been downregulated in ovariectomized and 17 β -estradiol-treated C57/BL6 mice, resulting in decreased abdominal fat accumulation [146]. Estrogens have been shown to reduce susceptibility to steatosis in liver cells of ovariectomized HFD-fed female mice [140]. Meanwhile, other study in mice have demonstrated that HFD leads to weight gain in males and females, with males exhibiting higher ceramide and phospholipid levels, renal lipotoxic-

ity, and decreased renal adiponectin and AMPK pathway activation [147]. Transcription of the *PLIN* gene, which regulates the formation of LDs, is activated by estrogen receptor-associated orphan nuclear receptors (ERR) α and regulates energy metabolism in a hormone-dependent manner [148].

In perimenopausal and postmenopausal women with decreased estrogen production and an indirect decrease in insulin sensitivity [149], a redistribution of body fat and the development of metabolic disorders, including MASLD and CKMS [8], have been observed. Additionally, elevated testosterone levels in women have been shown to increase their risk of developing MASLD [150], while, in men, the same pathology is associated with low testosterone levels [151,152].

3.2 Changes in the Structure and Function of Organs in Metabolic Diseases Against the Background of Impaired Lipid Metabolism and the Formation of Lipid Droplets

3.2.1 Lipid Droplets in Kidney Diseases

The accumulation of LDs is a hallmark of CKD [152]. In the kidneys, lipids are deposited in the paranephric space, renal sinus and renal parenchyma. Excessive accumulation of fatty acids in the paranephric space is associated with CKD and may contribute to renal dysfunction, whose mechanism has not yet been deciphered [153,154]. Excess perirenal adipose tissue can compress the renal vasculature and renal parenchyma, which increases renal interstitial hydrostatic pressure and renin release, while lowering the glomerular filtration rate [154,155]. In addition, fat accumulation in the renal sinus adjacent to the renal vasculature can trigger the production of mediators, such as adipokines, proinflammatory cytokines, nitric oxide (NO), and ROS [156]. The accumulation of LDs and the dysfunction of the renal sinus contribute to renal inflammation. Notably, meta-inflammation, associated with obesity, plays a direct role, starting from visceral adipose tissue (secretion of leptin, interleukin (IL)6/10, tumor necrosis factor (TNF), c-reactive protein (CRP)) [157] and leading to fibrosis, hypertension, and the progression of CKD. It has been found that the kidney can be damaged by dyslipidemia, contributing to lipid accumulation and an imbalance between fatty acid supply and utilization [158]. In addition, LDs act as intracellular mechanical stressors that trigger inflammation and fibrosis in the renal parenchyma [159]. Thus, progressive renal dysfunction is associated with the deposition of fat and LD in the renal cortex and medulla (parenchyma), which leads to the development of glomerulosclerosis, interstitial fibrosis, and proteinuria [152]. The epithelium of the renal tubules is the site of lipid deposition in HFD, characterized by the presence of giant vacuoles of lysosomal/autophagosomal origin, containing oxidized lipoproteins and multilayered bodies. These bodies have a lipid profile that differs from that of cytoplasmic LDs [160]. Excessive deposition of LDs in podocytes leads to lipotoxicity, abnormal glucose/lipid metabolism, and cell

death [161,162]. This process is associated with inflammation, oxidative stress, ER stress, actin cytoskeleton reorganization, and IR [163]. FAs cause LDs to accumulate lipids by direct uptake or by stimulating the biosynthesis of other FAs. Oxidative stress has been found to induce the formation of oxidized lipoproteins and changes in the TG profile in renal LDs, similar to that in hepatocytes in steatohepatitis. Changes in lipid metabolism lead to a decrease in polyunsaturated fatty acids (PUFAs) in the kidneys, which have a protective effect on the cytoplasmic matrix of cells. Excess PE results in a decreased PC/phosphatidylethanolamine (PE) ratio, while promoting the localization of PLIN on the surface of LDs, furthering the accumulation of lipids, and stimulating the growth of LDs [9]. It has been demonstrated that a high concentration of urea toxin as a result of impaired urea excretion can exacerbate adipose tissue inflammation and increase intestinal permeability, contributing to systemic and renal dysfunction. Moreover, PPAR γ , which regulates inflammatory processes, is highly expressed in the kidneys, as well as in the liver and adipose tissue. Obesity-associated changes in PPAR γ activity promote the accumulation of LDs in the kidneys, causing inflammation and fibrogenesis [164] and accelerating the systemic progression of MASLD and CKD. In contrast, MASLD and CKD are characterized by intestinal dysbiosis [165] associated with the loss of tight junctions between enterocytes. This facilitates the flow of lipopolysaccharides into the bloodstream, triggering inflammatory pathways (nuclear factor kappa B (NF- κ B), Toll-like receptor (TLR) 2, TLR4) in the liver and kidney and promoting fibrosis [120].

3.2.2 Lipid Droplets in Cardiovascular Diseases

Dysfunction in the storage and turnover of endogenous TG in LDs cardiomyocytes is linked to impaired transcriptional regulation of metabolic gene expression in heart failure. This dysfunction also results in reduced mitochondrial energy production, which is necessary to sustain cells and meet the energy demands of the contractile apparatus [166,167]. In addition, LDs can prevent lipid lipotoxicity by sequestering toxic lipid species: cholesterol, ceramides, and DAG [168]. The accumulation of cholesterol esters (CE) in LDs of macrophages (foam cells) in arteries precedes the development of atherosclerosis.

Although PLIN5 has been reported to accumulate nLDs in cardiomyocytes from starved mice, the ability of PLIN5 to regulate gene expression in the heart remains unclear [168]. Reduced *PLIN5* expression in the heart correlates with impaired cardiac function [169,170]. *PLIN5* gene knockout in mice has been shown to result in the absence of LDs in the heart muscle and the development of cardiomyopathy [171]. Overexpression of *PLIN5* in the heart is associated with cardiac steatosis and cardiac hypertrophy [172].

Intracellular accumulation of toxic lipid metabolites leads to cellular abnormalities that promote cardiac remodeling and cardiac dysfunction. Moreover, FA from the

bloodstream, along with LD, supply the heart with nutrients and support its functions. Excessive supply of FA to the heart is associated with a decrease in left ventricular function [173], LA accumulation, and the development of cardiac steatosis. The accumulation of LA in cardiac myocytes has been linked to obesity-related heart failure, T2DM, and hyperlipidemia [168,174]. Other consequences include the activation of PPAR γ [166], induction of the expression of genes involved in long-chain fatty acid (LCFA) uptake, β -oxidation enzymes, and TAG synthesis/lipolysis, ultimately resulting in oxidative stress and ceramide formation due to the limited lipid storage capacity of cardiac cells [168]. Excessive accumulation of lipids in vascular smooth muscle cells (VSMCs) can lead to their transformation into foam cells within atherosclerotic plaques. These foam cells trans-differentiate into macrophage-like cells and are characterized by the presence of CE-LDs [168,175,176].

3.2.3 Lipid Droplets in Hypothalamic Inflammation

The brain is able to detect circulating nutrients, hormones, and adipokines released by metabolically active tissues, such as the liver and adipose tissue, and initiates appropriate metabolic and behavioral responses to achieve metabolic homeostasis. The neuroendocrine regulation of energy balance takes place in various metabolically sensitive neuronal subpopulations of the hypothalamus. Altered lipid supply to the brain during HFD blunts the function of hypothalamic neurons and impairs their response to food signals, intragastric nutrients, neuropeptides, and adipokines [177]. Hypothalamic microglia control lipid metabolism and are involved in the development of IR [178]. Glia-like tanycytes lining the 3rd ventricle of the hypothalamus are known to serve as an interface between circulating metabolites (in blood and cerebrospinal fluid (CSF)) and energy-sensing hypothalamic neurons [179–181]. In response to an increase in circulating FAs, tanycytes secrete mediators that modulate neuronal activity and peripheral energy balance. In addition, tanycytes and astrocytes in the hypothalamus exhibit distinct mechanisms for perceiving lipids [182,183]. Astrocytes are a major source of brain lipoproteins that transport lipids to neurons and other glial cells, contributing to systemic energy balance [184]. They regulate the function of microglia and macrophages in the brain via horizontal lipoprotein flow [185]. In the context of elevated FA and saturated FA, lipid cross-talk between astrocytes, microglia and tanycytes promotes hypothalamic inflammation hypothalamic reactive gliosis [186,187]. Lipoprotein lipase has been shown to play an important role in the regulation of central energy homeostasis by astrocytes. Moreover, it is downregulated in the hypothalamus by palmitic acid and TGs, leading to decreased LDs, excessive weight gain, and glucose intolerance in mice [188,189]. Microglia are also able to remove unwanted lipids in the brain and promote lipid recycling through cholesterol efflux [190]. A model has been proposed describing horizontal lipid flow from microglia

to oligodendrocytes, the primary myelinating cells in the brain, which utilize glia-derived lipids to myelinate axons and regulate neuronal function [191]. Oligodendrocytes in the hypothalamus are regulated by diet, leading to changes in food intake and weight gain [192].

HFD-induced malnutrition is associated with the development of triglyceridemia, which, in turn, is associated with obesity, T2DM, and aging, leading to neuroinflammation, cognitive impairment, and neurodegeneration [192,193]. Chronic activation of microglia and the overproduction of inflammatory mediators lead to the expression of costimulatory molecules, neuronal dysfunction and apoptosis, loss of dendritic complexity, reduced number of synapses, and decreased synaptic plasticity key components of neuroinflammation [194,195]. Autophagy has been shown to play an important role in the normal function of brain cells. Impairment of autophagy leads to an accumulation of glial lipids in the form of LDs, a feature characteristic of aging. Hypothalamic lipotoxicity is inextricably linked to inflammation and reactive gliosis, contributing to leptin resistance, insulin resistance, and obesity [196,197]. Specifically, aged mice have shown an increase in the number and density of brain cells containing lipids in certain brain regions, leading to neurodegeneration [198]. In cases of mitochondrial dysfunction, a distinct population of senescent glial cells has been identified as promoting lipid deposition in non-senescent glial cells (observed in *Drosophila*). Similar effects have been observed in senescent human fibroblast cultures [199], with the accumulation of senescent glial cells contributing to the development of age-related diseases [200]. Moreover, inflammatory signaling has been shown to induce the accumulation of LDs in an activator protein 1 (AP1)/Jun2-dependent manner [201]. An inextricable link has been established between oxidative stress, mitochondrial dysfunction, and the accumulation of lipids during aging in brain neurons [202,203]. Notably, lipids can play a protective role against oxidative stress, which has been observed in AP⁺ glia that secrete lipids that are taken up and accumulated by AP[−] glia [201]. Senescent glial cells also accumulate lipids in the subventricular zone, including regions around the lateral ventricles, third ventricle, fourth ventricle, and periventricular gray matter [204].

The combination of LD protein/lipid composition and lipid flux through the LD storage pool is considered the best indicator of cell function, as it regulates signaling and lipid storage capacity to prevent lipotoxicity at high lipid concentrations [201]. The ARC of the hypothalamus contains populations of neurons involved in insulin resistance, while 3V tanycytes control systemic energy metabolism [205–207]. In low lipoprotein receptor-deficient (*Ldlr*^{−/−}) mice fed an HFD, heterogeneous deposition of LDs has been observed along the 3V ependymal layer at three rostral-caudal levels (suprachiasmatic nucleus (SCN); periventricular nucleus, paraventricular nucleus of the hypothalamus (PVH); arcuate nucleus, ARC) and three ventricular regions (superior, middle, and inferior) [208]. Most astrocytes and α 2-

tanycytes projecting to the ventromedial region of the ARC have been found to lack LDs, while $\alpha 2$ -tanycytes projecting to the dorsal region of the ARC have shown substantial amounts of LDs (PLIN2+) [208]. Similar results on the deposition of LDs in the ependymal of 3V in obese mice have been summarized by Wang and Li [180]. Moreover, alterations in lipid metabolism and LD content in tanycytes have been observed in obese mice [209]. Mouse tanycytes have also been demonstrated to change their gene expression patterns in response to fasting, showing functional diversity and plasticity [210]. Mouse tanycytes localized to the ARC region (α -tanycytes) have been shown to be sensitive to oxidative palmitate and capable of modulating neurons by indirectly blocking lipolysis in the periphery [211]. A study of postmortem hypothalamic tissue samples from patients with T2DM (n = 17) and without T2DM (n = 8) has revealed LDs content in ependymal cells in the 3V wall similar to LDs distribution in mice, with a predominance in the upper and middle regions: PVH and dorsomedial hypothalamic nucleus (DMH). This content was more pronounced in the group of patients without diabetes [208]. However, while increased LD expression has been observed in the hypothalamus in the mouse model of metabolic disorders, lower LD levels have been found in the hypothalamus in humans with T2DM compared to the control group [208]. In this case, it is important to consider the different ages of the human subjects (control group: 65–95 years old, patients with T2DM: 67–93 years old), the absence of a complete disease epicrisis, the presence of a significant number of cancers (n = 8), and the complexity and multifactorial nature of human pathologies compared to laboratory animals. Additionally, the presence of specialized areas in the human brain, such as the ARC, which are sensitive to lipids but do not accumulate lipid droplets, should also be taken into account [208]. In the past, aging and Alzheimer's disease were found to have significant amounts of LDs in the ependymal layer of brain ventricles, which correlated with the pathological conditions [198,212,213]. More recently, it has been suggested that tanycytes alone may accumulate LDL in response to HFD [209], contradicting the results of the earlier study and indicating a key role of tanycytes and ependymocytes in the accumulation of LDL and brain lipid metabolism in relation to nutritional conditions, concomitant diseases, and aging [208]. Damage to tanycytes impairs their anti-obesity effect on food intake, fat mass, and body weight [214,215]. Based on experimental data, it is hypothesized that the deposition of LDs in tanycytes (in mice) is linked to impaired hormone transmission from peripheral organs to the brain. This disruption leads to a compromised satiety signal transmission through leptin and insulin to POMC neurons, accompanied by decreased post-synaptic responses. As a result, autonomic synaptic nerve outflow becomes dysregulated, signaling in the PVH is inhibited, and hyperphagia develops [180,216,217].

In astrocytoma cells, FA-binding protein 7 (FABP7) and oleic acids can accelerate the formation of LDs-PML-

NB nuclear complexes and increase the expression of genes related to tumor proliferation [149]. Overexpression of FABP7 in the U87 astrocytoma cell line results in a higher accumulation of LDs and greater expression of antioxidant enzymes [150]. In addition, FABP7 has been shown to play a protective role against toxic oxygen species (ROS) in astrocytes through the formation of LDs. Specifically, in primary astrocytes from *FABP7* knockout mice, ROS induction has led to a significant reduction in LDs accumulation, accompanied by increased ROS toxicity, impaired thioredoxin (TRX) signaling, activation of p38 mitogen-activated protein kinase (MAPK) and stress-activated protein kinase/c-Jun N-terminal kinase (SAPK/JNK), and increased expression of cleaved caspase 3, ultimately leading to astrocyte apoptosis [150].

3.2.4 Lipid Droplets in the Pathogenesis of Liver Diseases (MASLD)

Obesity and MetS have a detrimental effect on liver health and contribute to the development of simple steatosis, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, cirrhosis and hepatocellular carcinoma [218].

An examination of 583 hepatocytes from a liver biopsy of a patient with moderate steatosis infected with hepatitis C virus (HCV) genotype 1b (chronic hepatitis grade A1-F1) revealed 402 cells with isolated cLDs and 64 cells with LDs localized within the nucleus. Sixty of these cells had deformed nuclei due to the presence of large cLDs or the presence of cLDs within the nucleus that were partially surrounded by the nuclear membrane, while 4 cells contained true nLDs [95]. The presence of cLDs within the nucleus may be explained by the perinuclear location of the ER, which is an extension of the nuclear envelope that facilitates their uptake by nuclear envelope invagination [95].

True nLDs, which are specific subdomains within the nucleus that store nuclear lipids, may regulate lipid homeostasis in the nucleus through their interaction with heterochromatin [95].

As mentioned above, nLDs, which are present in approximately 1% of cells, can directly regulate nuclear lipid metabolism, signaling, and interaction with FA-ligated transcription factors, such as *PPAR*, *HNF4 α* [219].

nLDs have been detected in HepG2 cells and in nuclei of hepatocytes isolated from rat liver. These nLDs consisted of 37% lipids and 63% proteins, with 19% TAG (oleic, linoleic and palmitic acids), 39% cholesterol esters, 27% C, and 15% polar lipids. In contrast, cLDs contained 91% TAG. The study has demonstrated that nLDs are an intranuclear domain that contains neutral lipids and is involved in lipid homeostasis in the nucleus [75]. They had a random intranuclear distribution in the size of several small droplets [75]. A study of liver biopsies from 80 patients with hepatopathologies of different etiologies has also shown the presence of several types of nLDs in hepatocytes [74]. nLDs were detected in 69% of the liver samples, while cLDs localized in the nucleus were observed in 32%.

MASH was associated with the highest percentage of nLDs in the hepatocytes and the absence of cLDs in the nuclei. There was a correlation between the expansion of the ER lumen, which forms against the background of ER stress, and the frequency of nLD formation in the hepatocytes. According to the results of the study, ER stress associated with liver enlargement was linked to the formation of nLDs in 5–10% of hepatocytes. cLDs in the nucleoplasm have been frequently identified in hepatocytes from patients with low plasma cholesterol levels, with their formation correlating inversely with the secretion of very VLDL [74].

Thus, there are two types of nLDs in hepatocytes that are associated with different liver diseases, such as MASH, drug-induced liver intoxication, and chronic autoimmune hepatitis. In hepatocytes, lipids stored in cLDs can be released by lipolysis and recycled in the ER lumen to generate VLDL precursors [220,221]. Suppression of VLDL secretion by ER stress leads to the accumulation of LDs precursors in the ER and their transfer (eLDs) to the nucleus via type-I NR invagination, followed by conversion of eLDs to nLDs after exiting the INM [37,78].

Lipin, a member of the PA phosphatase family, is associated with unregulated PA accumulation in the INM, leading to the binding of lipin-1b to the nuclear envelope (NE) and the formation of nLDs in U2OS cells [82]. A recent study in animals (McArdle's RH7777 rat liver cell lines, McA cells) with FITM2 protein deficiency (*Fitm2* gene deletion) (in mice) has shown that, under high-calorie diet conditions, plasma TG levels decrease while TG accumulates in the ER, leading to impaired ER morphology and ER stress [222]. These changes may also be associated with increased formation of nLDs in hepatocytes and enhanced expression of the PML protein, which was not investigated in the work presented [222].

In liver cells, nuclear lipids are located in nuclear membranes and in the nuclear matrix free of nuclear membranes. Although, in this case, polar nuclear lipids (glycerophospholipids) are mainly located in nuclear membranes, 10% of the lipids are associated with chromatin [75]. The Kennedy pathway mediates the synthesis of glycerophospholipids with the formation of PC through the catalytic reaction of the enzyme CCT α , which is encoded by the *PCYT1A* gene and acts as a sensor for low PC content in the nuclear envelope [223]. nLDs can serve as a platform for PC synthesis under conditions of oleic acid overload by recruiting CCT α [81,224,225], leading to enhanced membrane synthesis and ER volume expansion, and counteracting ER stress [226] in human cell lines (U2OS, HeLa, Caco2) [224]. In addition, localization of CCT α and INM leads to the growth of intranuclear structures containing glycerophospholipids type-I NR [227,228] and nLDs [37,81,82,229]. This suggests that the formation of nLDs is linked to a mechanism that reduces ER stress through the increased synthesis of PC in liver disease.

Studies in hepatocytes and U2OS cells have shown that nLDs contain enzymes that regulate TAG synthesis,

including DGAT1/DGAT2, AGPAT2, GPAT3/GPAT4, and acyl-CoA synthetase long-chain 3 (ACSL3) [37,78].

cLDs in the nucleus of hepatocytes, which are sequestered in type-II NR and separated from the ER, can restrict the transfer of lipids between organelles, leading to a decrease in lipoprotein synthesis in the liver in patients with low plasma sterol levels [74]. Presumably, sterols are sequestered to a high degree in cell membranes (in the nucleus), which leads to the deposition of the ONM and INM in hepatocytes. In the case of severe steatosis (20%), in hepatocytes with an abundance of cLDs, cholesterol accumulates in the form of cholesterol esters in cLDs, inhibiting the formation of cLDs that are scavenged by type-II NR [74]. This hypothesis has been supported by the study conducted by Liu *et al.* (2023) [230] on freshwater fish (*Gobiocypris rarus*) from China exposed to cadmium. The study has established a link between liver injury and the accumulation of cLDs, cLDs in the nucleus, and the appearance of nLDs, all against the background of abnormal increase in rough ER lamellae (RER), hepatocyte necrosis, a rise in serum levels of total cholesterol, triglycerides and lipids. However, there was no alteration in the transcription of the *PPAR α* gene mRNA [230]. An accumulation of cLDs and nLDs in the liver has been observed in severe lipid metabolism disorders [230].

Thus, NE lipid imbalance caused by overload of cells with lipotoxic FAs may induce the formation of nLDs as a mechanism to reduce the deleterious effects of FAs, and minimize the risk of losing NE homeostasis [33]. In addition, this mechanism of nLD formation may be triggered in response to genotoxic drug-induced impairment of DNA replication, contributing to the slowing/silencing of replication fork activity [77,230].

It has been found that long-term chronic liver injury caused by MASLD can lead to the proliferation of certain hepatocytes in an attempt to maintain liver homeostasis [231].

4. Conclusions

MetS is a multi-component pathological condition leading to the dysfunction of cells, organs, and body systems. It is associated with the development of more severe pathologies affecting the organs and systems of the body, such as MASLD and CKMS. The discovery of new, unique nuclear structures specific to certain cell types and involved in lipid metabolism, known as nLDs, has drawn the attention of scientists to their organization, formation, and biogenesis in cells. However, the available data on both normal and pathological conditions is insufficient to fully explain the existence of nLDs or determine their exact role in cells. At the same time, experimental research on nLDs has advanced sufficiently to allow for discussions on the critical role of these organelles in diseases linked to energy imbalance, aging, and the lipotoxic effects of excess fatty acids. These factors contribute to the development of obesity, liver and vascular diseases,

kidney pathologies, brain inflammation, and other components of MetS, MASLD, and CKMS. The close association of LDs with the nucleus may indicate different roles of nLDs in hepatocytes and brain cells, including their involvement in the metabolism of phosphatidic acid [76,82], phosphatidylcholine [37,81,82,229], triglycerides, as well as their response to genotoxic drugs [77,230], interaction and regulation of heterochromatin [75], induction of cellular senescence, and provision of readily available FAs for the nuclear membrane [75]. This confirms that the formation of LDs within the nucleus is compensatory and anti-toxic; it helps maintain the functional capacity of the nuclear membrane, reduce ER stress [222], and preserve the integrity of the cell under conditions of metabolic disturbances, contributing to the development and progression of metabolic diseases. A deeper and more detailed study of intranuclear structures, along with a better understanding of the functioning of nLDs, will enable the identification of specific, pathogenetically-based targets for combating metabolic disorders.

Abbreviations

FA, fatty acids; MetS, metabolic syndrome; IR, insulin resistance; HFD, high-fat/high-calorie diet; ROS, reactive oxygen species; ER, endoplasmic reticulum; TG, triglyceride; TAG, triacylglycerol; DAG, diacylglycerol; LD, lipid droplet; eLD, luminal lipid droplet; cLD, cytoplasmic lipid droplet; nLD, nuclear lipid droplet; AgRP, agouti-related protein neurons; POMC, proopiomelanocortin; ARC, arcuate nucleus; PVH, paraventricular nucleus of the hypothalamus; MBH, mediobasal nucleus; SCN, suprachiasmatic nucleus; ACC, Acetyl-CoA carboxylase; CPT-1, carnitine palmitoyltransferase-1; GPAT, glycerol phosphate acyltransferase; AGPAT, acyl glycerol phosphate acyltransferase; PA, phosphatidic acid; PAP, phosphatidic acid phosphohydrolase; DGAT, acyl-CoA:diacylglycerol acyltransferase; SE, steryl ester; PKA, protein kinase A; ONM, outer nuclear membrane; INM, inner nuclear membrane; NR, nucleoplasmic reticulum; CCT α , phosphocholine cytidyltransferase α ; PML NB, promyelocytic leukemia nuclear bodies; LBR, lamin B receptor; Pah1, phosphatidic acid phosphohydrolase 1; Cds1, phosphatidate cytidyltransferase; MTP, microsomal triglyceride transfer protein; PC, phosphatidylcholine; PLIN, perilipin; NE, nuclear envelope; RER, rough ER lamellae; NAFLD, non-alcoholic fatty liver disease; T2DM, type 2 diabetes mellitus; FABP7, FA-binding protein 7; VLDL, very low-density lipoproteins; MASLD, metabolic dysfunction-associated hepatic steatosis; CKD, chronic kidney disease; CKMS, cardiovascular-kidney-metabolic syndrome.

Author Contributions

Acquisition, analysis and interpretation of data for the work NT, KY, MV, OK, AK, VM; Writing the paper NT; Editing and reviewing the original article LL, IKo, IKh; study concept or design NT, LL, IKo, IKh; project admin-

istrator, LL. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

All drawings were created by a team of authors using the Biorender program.

Funding

This work was supported by the Russian Science Foundation (project no. 23-15-00061).

Conflict of Interest

The authors declare no conflict of interest.

References

- [1] Todosenko N, Khaziakhmatova O, Malashchenko V, Yurova K, Bograya M, Beletskaya M, *et al.* Adipocyte- and Monocyte-Mediated Vicious Circle of Inflammation and Obesity (Review of Cellular and Molecular Mechanisms). *International Journal of Molecular Sciences*. 2023; 24: 12259. <https://doi.org/10.3390/ijms241512259>.
- [2] Todosenko N, Vulf M, Yurova K, Khaziakhmatova O, Mikhailova L, Litvinova L. Causal Links between Hypovitaminosis D and Dysregulation of the T Cell Connection of Immunity Associated with Obesity and Concomitant Pathologies. *Biomedicine*. 2021; 9: 1750. <https://doi.org/10.3390/biomedines9121750>.
- [3] Litvinova L, Vulf M, Yurova K, Khaziakhmatova O, Malashchenko V, Bograya M, *et al.* Mitochondria and Lipid Droplets: Focus on the Molecular Structure of Contact Sites in the Pathogenesis of Metabolic Syndrome. *Current Medicinal Chemistry*. 2024; 10.2174/0109298673309247240610050423. <https://doi.org/10.2174/0109298673309247240610050423>.
- [4] Todosenko N, Vulf M, Yurova K, Skuratovskaia D, Khaziakhmatova O, Gazatova N, *et al.* The Pathogenic Subpopulation of Th17 Cells in Obesity. *Current Pharmaceutical Design*. 2021; 27: 3924–3938. <https://doi.org/10.2174/1381612826666210101154913>.
- [5] Todosenko N, Yurova K, Vulf M, Khaziakhmatova O, Litvinova L. Prohibitions in the meta-inflammatory response: a review. *Frontiers in Molecular Biosciences*. 2024; 11: 1322687. <https://doi.org/10.3389/fmolb.2024.1322687>.
- [6] Todosenko N, Khaziakhmatova O, Malashchenko V, Yurova K, Bograya M, Beletskaya M, *et al.* Mitochondrial Dysfunction Associated with mtDNA in Metabolic Syndrome and Obesity. *International Journal of Molecular Sciences*. 2023; 24: 12012. <https://doi.org/10.3390/ijms241512012>.
- [7] Vulf M, Khlusov I, Yurova K, Todosenko N, Komar A, Kozlov I, *et al.* MicroRNA Regulation of Bone Marrow Mesenchymal Stem Cells in the Development of Osteoporosis in Obesity. *Frontiers in Bioscience (Scholar Edition)*. 2022; 14: 17. <https://doi.org/10.31083/j.fbs1403017>.
- [8] Cen C, Fan Z, Ding X, Tu X, Liu Y. Associations between metabolic dysfunction-associated fatty liver disease, chronic kidney disease, and abdominal obesity: a national retrospec-

- tive cohort study. *Scientific Reports*. 2024; 14: 12645. <https://doi.org/10.1038/s41598-024-63386-0>.
- [9] Chen Z, Shrestha R, Yang X, Wu X, Jia J, Chiba H, *et al*. Oxidative Stress and Lipid Dysregulation in Lipid Droplets: A Connection to Chronic Kidney Disease Revealed in Human Kidney Cells. *Antioxidants* (Basel, Switzerland). 2022; 11: 1387. <https://doi.org/10.3390/antiox11071387>.
- [10] Ndumele CE, Neeland IJ, Tuttle KR, Chow SL, Mathew RO, Khan SS, *et al*. A Synopsis of the Evidence for the Science and Clinical Management of Cardiovascular-Kidney-Metabolic (CKM) Syndrome: A Scientific Statement From the American Heart Association. *Circulation*. 2023; 148: 1636–1664. <https://doi.org/10.1161/CIR.0000000000001186>.
- [11] Weihrach-Blüher S, Schwarz P, Klusmann JH. Childhood obesity: increased risk for cardiometabolic disease and cancer in adulthood. *Metabolism: Clinical and Experimental*. 2019; 92: 147–152. <https://doi.org/10.1016/j.metabol.2018.12.001>.
- [12] Lega IC, Lipscombe LL. Review: Diabetes, Obesity, and Cancer-Pathophysiology and Clinical Implications. *Endocrine Reviews*. 2020; 41: bnz014. <https://doi.org/10.1210/endrev/bnz014>.
- [13] Hopkins BD, Goncalves MD, Cantley LC. Obesity and Cancer Mechanisms: Cancer Metabolism. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*. 2016; 34: 4277–4283. <https://doi.org/10.1200/JCO.2016.67.9712>.
- [14] Wilson RL, Taaffe DR, Newton RU, Hart NH, Lyons-Wall P, Galvão DA. Obesity and prostate cancer: A narrative review. *Critical Reviews in Oncology/hematology*. 2022; 169: 103543. <https://doi.org/10.1016/j.critrevonc.2021.103543>.
- [15] Franchini F, Palatucci G, Colao A, Ungaro P, Macchia PE, Nettore IC. Obesity and Thyroid Cancer Risk: An Update. *International Journal of Environmental Research and Public Health*. 2022; 19: 1116. <https://doi.org/10.3390/ijerph19031116>.
- [16] Iyengar NM, Gucalp A, Dannenberg AJ, Hudis CA. Obesity and Cancer Mechanisms: Tumor Microenvironment and Inflammation. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*. 2016; 34: 4270–4276. <https://doi.org/10.1200/JCO.2016.67.4283>.
- [17] Lee K, Kruper L, Dieli-Conwright CM, Mortimer JE. The Impact of Obesity on Breast Cancer Diagnosis and Treatment. *Current Oncology Reports*. 2019; 21: 41. <https://doi.org/10.1007/s11912-019-0787-1>.
- [18] Tan SK, Hougen HY, Merchan JR, Gonzalgo ML, Welford SM. Fatty acid metabolism reprogramming in ccRCC: mechanisms and potential targets. *Nature Reviews. Urology*. 2023; 20: 48–60. <https://doi.org/10.1038/s41585-022-00654-6>.
- [19] Todosenko N, Yurova K, Khaziakhmatova O, Vulf M, Bograya M, Ivanov P, *et al*. (Epi) genetic Aspects of Metabolic Syndrome Pathogenesis in Relation to Brain-derived Neurotrophic Factor Expression: A Review. *Gene Expression*. 2024; 23: 127–138.
- [20] Seong J, Kang JY, Sun JS, Kim KW. Hypothalamic inflammation and obesity: a mechanistic review. *Archives of Pharmacological Research*. 2019; 42: 383–392. <https://doi.org/10.1007/s12272-019-01138-9>.
- [21] Yoon NA, Diano S. Hypothalamic glucose-sensing mechanisms. *Diabetologia*. 2021; 64: 985–993. <https://doi.org/10.1007/s00125-021-05395-6>.
- [22] Manceau R, Majeur D, Alquier T. Neuronal control of peripheral nutrient partitioning. *Diabetologia*. 2020; 63: 673–682. <https://doi.org/10.1007/s00125-020-05104-9>.
- [23] Sewaybricker LE, Huang A, Chandrasekaran S, Melhorn SJ, Schur EA. The Significance of Hypothalamic Inflammation and Gliosis for the Pathogenesis of Obesity in Humans. *Endocrine Reviews*. 2023; 44: 281–296. <https://doi.org/10.1210/endrev/bnac023>.
- [24] Lee CH, Kim HJ, Lee YS, Kang GM, Lim HS, Lee SH, *et al*. Hypothalamic Macrophage Inducible Nitric Oxide Synthase Mediates Obesity-Associated Hypothalamic Inflammation. *Cell Reports*. 2018; 25: 934–946.e5. <https://doi.org/10.1016/j.celrep.2018.09.070>.
- [25] Okekawa A, Wada T, Onogi Y, Takeda Y, Miyazawa Y, Sashihara M, *et al*. Platelet-derived growth factor signaling in pericytes promotes hypothalamic inflammation and obesity. *Molecular Medicine* (Cambridge, Mass.). 2024; 30: 21. <https://doi.org/10.1186/s10020-024-00793-z>.
- [26] Waterson MJ, Horvath TL. Neuronal Regulation of Energy Homeostasis: Beyond the Hypothalamus and Feeding. *Cell Metabolism*. 2015; 22: 962–970. <https://doi.org/10.1016/j.cmet.2015.09.026>.
- [27] Folick A, Cheang RT, Valdearcos M, Koliwad SK. Metabolic factors in the regulation of hypothalamic innate immune responses in obesity. *Experimental & Molecular Medicine*. 2022; 54: 393–402. <https://doi.org/10.1038/s12276-021-00666-z>.
- [28] Wolfgang MJ, Cha SH, Sidhaye A, Chohann S, Cline G, Shulman GI, *et al*. Regulation of hypothalamic malonyl-CoA by central glucose and leptin. *Proceedings of the National Academy of Sciences of the United States of America*. 2007; 104: 19285–19290. <https://doi.org/10.1073/pnas.0709778104>.
- [29] Taïb B, Bouyakdan K, Hryhorczuk C, Rodaros D, Fulton S, Alquier T. Glucose regulates hypothalamic long-chain fatty acid metabolism via AMP-activated kinase (AMPK) in neurons and astrocytes. *The Journal of Biological Chemistry*. 2013; 288: 37216–37229. <https://doi.org/10.1074/jbc.M113.506238>.
- [30] Xu S, Zhang X, Liu P. Lipid droplet proteins and metabolic diseases. *Biochimica et Biophysica Acta. Molecular Basis of Disease*. 2018; 1864: 1968–1983. <https://doi.org/10.1016/j.bbadis.2017.07.019>.
- [31] Zadoorian A, Du X, Yang H. Lipid droplet biogenesis and functions in health and disease. *Nature Reviews. Endocrinology*. 2023; 19: 443–459. <https://doi.org/10.1038/s41574-023-00845-0>.
- [32] Jackson CL. Lipid droplet biogenesis. *Current Opinion in Cell Biology*. 2019; 59: 88–96. <https://doi.org/10.1016/j.ccb.2019.03.018>.
- [33] Fujimoto T. Nuclear lipid droplet: Guardian of nuclear membrane lipid homeostasis? *Current Opinion in Cell Biology*. 2024; 88: 102370. <https://doi.org/10.1016/j.ccb.2024.102370>.
- [34] Zhang Z, Yu Z, Liang D, Song K, Kong X, He M, *et al*. Roles of lipid droplets and related proteins in metabolic diseases. *Lipids in Health and Disease*. 2024; 23: 218. <https://doi.org/10.1186/s12944-024-02212-y>.
- [35] Renne MF, Klug YA, Carvalho P. Lipid droplet biogenesis: A mystery “unmixing”? *Seminars in Cell & Developmental Biology*. 2020; 108: 14–23. <https://doi.org/10.1016/j.semcdb.2020.03.001>.
- [36] McPhee MJ, Salsman J, Foster J, Thompson J, Mathavarajah S, Delleire G, *et al*. Running ‘LAPS’ Around nLD: Nuclear Lipid Droplet Form and Function. *Frontiers in Cell and Developmental Biology*. 2022; 10: 837406. <https://doi.org/10.3389/fcell.2022.837406>.
- [37] Ohsaki Y, Kawai T, Yoshikawa Y, Cheng J, Jokitalo E, Fujimoto T. PML isoform II plays a critical role in nuclear lipid droplet formation. *The Journal of Cell Biology*. 2016; 212: 29–38. <https://doi.org/10.1083/jcb.201507122>.
- [38] Farese RV, Jr, Walther TC. Lipid droplets go nuclear. *The Journal of Cell Biology*. 2016; 212: 7–8. <https://doi.org/10.1083/jcb.201512056>.
- [39] Wilfling F, Haas JT, Walther TC, Farese RV, Jr. Lipid droplet biogenesis. *Current Opinion in Cell Biology*. 2014; 29: 39–45. <https://doi.org/10.1016/j.ccb.2014.03.008>.
- [40] Henne M, Goodman JM, Hariri H. Spatial compartmentalization of lipid droplet biogenesis. *Biochimica et Biophysica Acta. Molecular and Cell Biology of Lipids*. 2020; 1865: 158499. <https://doi.org/10.1016/j.bbalip.2019.07.008>.

- [41] Wilfling F, Wang H, Haas JT, Krahmer N, Gould TJ, Uchida A, *et al.* Triacylglycerol synthesis enzymes mediate lipid droplet growth by relocating from the ER to lipid droplets. *Developmental Cell*. 2013; 24: 384–399. <https://doi.org/10.1016/j.devcel.2013.01.013>.
- [42] Jacquier N, Choudhary V, Mari M, Toulmay A, Reggiori F, Schneider R. Lipid droplets are functionally connected to the endoplasmic reticulum in *Saccharomyces cerevisiae*. *Journal of Cell Science*. 2011; 124: 2424–2437. <https://doi.org/10.1242/jcs.076836>.
- [43] Goodman JM. Demonstrated and inferred metabolism associated with cytosolic lipid droplets. *Journal of Lipid Research*. 2009; 50: 2148–2156. <https://doi.org/10.1194/jlr.R001446>.
- [44] Coleman RA, Lee DP. Enzymes of triacylglycerol synthesis and their regulation. *Progress in Lipid Research*. 2004; 43: 134–176. [https://doi.org/10.1016/s0163-7827\(03\)00051-1](https://doi.org/10.1016/s0163-7827(03)00051-1).
- [45] Irshad Z, Dimitri F, Christian M, Zammit VA. Diacylglycerol acyltransferase 2 links glucose utilization to fatty acid oxidation in the brown adipocytes. *Journal of Lipid Research*. 2017; 58: 15–30. <https://doi.org/10.1194/jlr.M068197>.
- [46] Chitraju C, Walther TC, Farese RV, Jr. The triglyceride synthesis enzymes DGAT1 and DGAT2 have distinct and overlapping functions in adipocytes. *Journal of Lipid Research*. 2019; 60: 1112–1120. <https://doi.org/10.1194/jlr.M093112>.
- [47] Villanueva CJ, Monetti M, Shih M, Zhou P, Watkins SM, Bhanot S, *et al.* Specific role for acyl CoA:Diacylglycerol acyltransferase 1 (Dgat1) in hepatic steatosis due to exogenous fatty acids. *Hepatology (Baltimore, Md.)*. 2009; 50: 434–442. <https://doi.org/10.1002/hep.22980>.
- [48] Nguyen TB, Louie SM, Daniele JR, Tran Q, Dillin A, Zoncu R, *et al.* DGAT1-Dependent Lipid Droplet Biogenesis Protects Mitochondrial Function during Starvation-Induced Autophagy. *Developmental Cell*. 2017; 42: 9–21.e5. <https://doi.org/10.1016/j.devcel.2017.06.003>.
- [49] Wang CW. Lipid droplet dynamics in budding yeast. *Cellular and Molecular Life Sciences: CMLS*. 2015; 72: 2677–2695. <https://doi.org/10.1007/s00018-015-1903-5>.
- [50] Olzmann JA, Carvalho P. Dynamics and functions of lipid droplets. *Nature Reviews. Molecular Cell Biology*. 2019; 20: 137–155. <https://doi.org/10.1038/s41580-018-0085-z>.
- [51] Chorlay A, Thiam AR. An Asymmetry in Monolayer Tension Regulates Lipid Droplet Budding Direction. *Biophysical Journal*. 2018; 114: 631–640. <https://doi.org/10.1016/j.bpj.2017.12.014>.
- [52] Chorlay A, Monticelli L, Verissimo Ferreira J, Ben M'barek K, Ajjaji D, Wang S, *et al.* Membrane Asymmetry Imposes Directionality on Lipid Droplet Emergence from the ER. *Developmental Cell*. 2019; 50: 25–42.e7. <https://doi.org/10.1016/j.devcel.2019.05.003>.
- [53] Duelund L, Jensen GV, Hannibal-Bach HK, Ejsing CS, Pedersen JS, Pakkanen KI, *et al.* Composition, structure and properties of POPC-triolein mixtures. Evidence of triglyceride domains in phospholipid bilayers. *Biochimica et Biophysica Acta*. 2013; 1828: 1909–1917. <https://doi.org/10.1016/j.bbamem.2013.03.020>.
- [54] Roux A, Loewith R. Tensing Up for Lipid Droplet Formation. *Developmental Cell*. 2017; 41: 571–572. <https://doi.org/10.1016/j.devcel.2017.06.001>.
- [55] Prinz WA. A bridge to understanding lipid droplet growth. *Developmental Cell*. 2013; 24: 335–336. <https://doi.org/10.1016/j.devcel.2013.02.004>.
- [56] Wilfling F, Thiam AR, Olarte MJ, Wang J, Beck R, Gould TJ, *et al.* Arf1/COPI machinery acts directly on lipid droplets and enables their connection to the ER for protein targeting. *eLife*. 2014; 3: e01607. <https://doi.org/10.7554/eLife.01607>.
- [57] Fei W, Shui G, Zhang Y, Krahmer N, Ferguson C, Kaptejian TS, *et al.* A role for phosphatidic acid in the formation of “supersized” lipid droplets. *PLoS Genetics*. 2011; 7: e1002201. <https://doi.org/10.1371/journal.pgen.1002201>.
- [58] Ben M'barek K, Ajjaji D, Chorlay A, Vanni S, Forêt L, Thiam AR. ER Membrane Phospholipids and Surface Tension Control Cellular Lipid Droplet Formation. *Developmental Cell*. 2017; 41: 591–604.e7. <https://doi.org/10.1016/j.devcel.2017.05.012>.
- [59] Choudhary V, Golani G, Joshi AS, Cottier S, Schneider R, Prinz WA, *et al.* Architecture of Lipid Droplets in Endoplasmic Reticulum Is Determined by Phospholipid Intrinsic Curvature. *Current Biology: CB*. 2018; 28: 915–926.e9. <https://doi.org/10.1016/j.cub.2018.02.020>.
- [60] Scorletti E, Carr RM. A new perspective on NAFLD: Focusing on lipid droplets. *Journal of Hepatology*. 2022; 76: 934–945. <https://doi.org/10.1016/j.jhep.2021.11.009>.
- [61] Mishra S, Khaddaj R, Cottier S, Stradalova V, Jacob C, Schneider R. Mature lipid droplets are accessible to ER luminal proteins. *Journal of Cell Science*. 2016; 129: 3803–3815. <https://doi.org/10.1242/jcs.189191>.
- [62] Hu J, Shibata Y, Zhu PP, Voss C, Rismanchi N, Prinz WA, *et al.* A class of dynamin-like GTPases involved in the generation of the tubular ER network. *Cell*. 2009; 138: 549–561. <https://doi.org/10.1016/j.cell.2009.05.025>.
- [63] Schneider R, Choudhary V. Seipin collaborates with the ER membrane to control the sites of lipid droplet formation. *Current Opinion in Cell Biology*. 2022; 75: 102070. <https://doi.org/10.1016/j.cob.2022.02.004>.
- [64] Prasanna X, Salo VT, Li S, Ven K, Vihinen H, Jokitalo E, *et al.* Seipin traps triacylglycerols to facilitate their nanoscale clustering in the endoplasmic reticulum membrane. *PLoS Biology*. 2021; 19: e3000998. <https://doi.org/10.1371/journal.pbio.3000998>.
- [65] Zoni V, Khaddaj R, Lukmantara I, Shinoda W, Yang H, Schneider R, *et al.* Seipin accumulates and traps diacylglycerols and triglycerides in its ring-like structure. *Proceedings of the National Academy of Sciences of the United States of America*. 2021; 118: e2017205118. <https://doi.org/10.1073/pnas.2017205118>.
- [66] Choudhary V, Ojha N, Golden A, Prinz WA. A conserved family of proteins facilitates nascent lipid droplet budding from the ER. *The Journal of Cell Biology*. 2015; 211: 261–271. <https://doi.org/10.1083/jcb.201505067>.
- [67] Wang G, Chen A, Wu Y, Wang D, Chang C, Yu G. Fat storage-inducing transmembrane proteins: beyond mediating lipid droplet formation. *Cellular & Molecular Biology Letters*. 2022; 27: 98. <https://doi.org/10.1186/s11658-022-00391-z>.
- [68] Gao M, Huang X, Song BL, Yang H. The biogenesis of lipid droplets: Lipids take center stage. *Progress in Lipid Research*. 2019; 75: 100989. <https://doi.org/10.1016/j.plipres.2019.100989>.
- [69] Chen F, Yan B, Ren J, Lyu R, Wu Y, Guo Y, *et al.* FIT2 organizes lipid droplet biogenesis with ER tubule-forming proteins and septins. *The Journal of Cell Biology*. 2021; 220: e201907183. <https://doi.org/10.1083/jcb.201907183>.
- [70] Goodman JM. LADF1 Holds the Key to Seipin Function. *Developmental Cell*. 2019; 51: 544–545. <https://doi.org/10.1016/j.devcel.2019.11.009>.
- [71] Chung J, Wu X, Lambert TJ, Lai ZW, Walther TC, Farese RV, Jr. LADF1 and Seipin Form a Lipid Droplet Assembly Complex. *Developmental Cell*. 2019; 51: 551–563.e7. <https://doi.org/10.1016/j.devcel.2019.10.006>.
- [72] Li X, Yang L, Mao Z, Pan X, Zhao Y, Gu X, *et al.* Novel role of dynamin-related-protein 1 in dynamics of ER-lipid droplets in adipose tissue. *FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology*. 2020; 34: 8265–8282. <https://doi.org/10.1096/fj.201903100RR>.
- [73] Adachi Y, Kato T, Yamada T, Murata D, Arai K, Stahelin RV, *et al.* Drp1 Tubulates the ER in a GTPase-Independent Manner. *Molecular Cell*. 2020; 80: 621–632.e6. <https://doi.org/10.1016/j.molcel.2020.05.012>.

- [74] Imai N, Ohsaki Y, Cheng J, Zhang J, Mizuno F, Tanaka T, *et al.* Distinct features of two lipid droplets types in cell nuclei from patients with liver diseases. *Scientific Reports*. 2023; 13: 6851. <https://doi.org/10.1038/s41598-023-33977-4>.
- [75] Layerenza JP, González P, García de Bravo MM, Polo MP, Sisti MS, Ves-Losada A. Nuclear lipid droplets: a novel nuclear domain. *Biochimica et Biophysica Acta*. 2013; 1831: 327–340. <https://doi.org/10.1016/j.bbalip.2012.10.005>.
- [76] Romanauska A, Köhler A. The Inner Nuclear Membrane Is a Metabolically Active Territory that Generates Nuclear Lipid Droplets. *Cell*. 2018; 174: 700–715.e18. <https://doi.org/10.1016/j.cell.2018.05.047>.
- [77] Kumanski S, Forey R, Cazevielle C, Moriel-Carretero M. Nuclear Lipid Droplet Birth during Replicative Stress. *Cells*. 2022; 11: 1390. <https://doi.org/10.3390/cells11091390>.
- [78] Sołtysik K, Ohsaki Y, Tatematsu T, Cheng J, Fujimoto T. Nuclear lipid droplets derive from a lipoprotein precursor and regulate phosphatidylcholine synthesis. *Nature Communications*. 2019; 10: 473. <https://doi.org/10.1038/s41467-019-08411-x>.
- [79] Palikaras K, Mari M, Ploumi C, Prinz A, Filippidis G, Tavernarakis N. Age-dependent nuclear lipid droplet deposition is a cellular hallmark of aging in *Caenorhabditis elegans*. *Aging Cell*. 2023; 22: e13788. <https://doi.org/10.1111/acel.13788>.
- [80] Corpet A, Kleijwegt C, Roubille S, Juillard F, Jacquet K, Texier P, *et al.* PML nuclear bodies and chromatin dynamics: catch me if you can!. *Nucleic Acids Research*. 2020; 48: 11890–11912. <https://doi.org/10.1093/nar/gkaa828>.
- [81] Lee J, Salsman J, Foster J, Dellaire G, Ridgway ND. Lipid-associated PML structures assemble nuclear lipid droplets containing CCT α and Lipin1. *Life Science Alliance*. 2020; 3: e202000751. <https://doi.org/10.26508/lsa.202000751>.
- [82] Sołtysik K, Ohsaki Y, Tatematsu T, Cheng J, Maeda A, Morita SY, *et al.* Nuclear lipid droplets form in the inner nuclear membrane in a seipin-independent manner. *The Journal of Cell Biology*. 2021; 220: e202005026. <https://doi.org/10.1083/jcb.202005026>.
- [83] Turgay Y, Champion L, Balazs C, Held M, Toso A, Gerlich DW, *et al.* SUN proteins facilitate the removal of membranes from chromatin during nuclear envelope breakdown. *The Journal of Cell Biology*. 2014; 204: 1099–1109. <https://doi.org/10.1083/jcb.201310116>.
- [84] Gallardo-Montejano VI, Saxena G, Kusminski CM, Yang C, McAfee JL, Hahner L, *et al.* Nuclear Perilipin 5 integrates lipid droplet lipolysis with PGC-1 α /SIRT1-dependent transcriptional regulation of mitochondrial function. *Nature Communications*. 2016; 7: 12723. <https://doi.org/10.1038/ncomms12723>.
- [85] Iqbal J, Jahangir Z, Al-Qarni AA. Microsomal Triglyceride Transfer Protein: From Lipid Metabolism to Metabolic Diseases. *Advances in Experimental Medicine and Biology*. 2020; 1276: 37–52. https://doi.org/10.1007/978-981-15-6082-8_4.
- [86] Syed-Abdul MM. Lipid Metabolism in Metabolic-Associated Steatotic Liver Disease (MASLD). *Metabolites*. 2023; 14: 12. <https://doi.org/10.3390/metabo14010012>.
- [87] Hussain MM, Rava P, Walsh M, Rana M, Iqbal J. Multiple functions of microsomal triglyceride transfer protein. *Nutrition & Metabolism*. 2012; 9: 14. <https://doi.org/10.1186/1743-7075-9-14>.
- [88] Wang S, Chen Z, Lam V, Han J, Hassler J, Finck BN, *et al.* IRE1 α -XBPs induces PDI expression to increase MTP activity for hepatic VLDL assembly and lipid homeostasis. *Cell Metabolism*. 2012; 16: 473–486. <https://doi.org/10.1016/j.cmet.2012.09.003>.
- [89] Jul-Larsen A, Grudic A, Bjerkvig R, Bøe SO. Subcellular distribution of nuclear import-defective isoforms of the promyelocytic leukemia protein. *BMC Molecular Biology*. 2010; 11: 89. <https://doi.org/10.1186/1471-2199-11-89>.
- [90] Lehner R, Lian J, Quiroga AD. Lumenal lipid metabolism: implications for lipoprotein assembly. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2012; 32: 1087–1093. <https://doi.org/10.1161/ATVBAHA.111.241497>.
- [91] Cornell RB, Ridgway ND. CTP:phosphocholine cytidyltransferase: Function, regulation, and structure of an amphitropic enzyme required for membrane biogenesis. *Progress in Lipid Research*. 2015; 59: 147–171. <https://doi.org/10.1016/j.plipres.2015.07.001>.
- [92] Merta H, Bahmanyar S. The Inner Nuclear Membrane Takes On Lipid Metabolism. *Developmental Cell*. 2018; 47: 397–399. <https://doi.org/10.1016/j.devcel.2018.11.005>.
- [93] Wang X, Han X, Powell CA. Lipids and genes: Regulatory roles of lipids in RNA expression. *Clinical and Translational Medicine*. 2022; 12: e863. <https://doi.org/10.1002/ctm2.863>.
- [94] Fernandes V, Teles K, Ribeiro C, Treptow W, Santos G. Fat nucleosome: Role of lipids on chromatin. *Progress in Lipid Research*. 2018; 70: 29–34. <https://doi.org/10.1016/j.plipres.2018.04.003>.
- [95] Uzbekov R, Roingeard P. Nuclear lipid droplets identified by electron microscopy of serial sections. *BMC Research Notes*. 2013; 6: 386. <https://doi.org/10.1186/1756-0500-6-386>.
- [96] Ha S, Wong VWS, Zhang X, Yu J. Interplay between gut microbiome, host genetic and epigenetic modifications in MASLD and MASLD-related hepatocellular carcinoma. *Gut*. 2024; 74: 141–152. <https://doi.org/10.1136/gutjnl-2024-332398>.
- [97] Sherman DJ, Liu L, Mamrosh JL, Xie J, Ferbas J, Lomenick B, *et al.* The fatty liver disease-causing protein PNPLA3-I148M alters lipid droplet-Golgi dynamics. *Proceedings of the National Academy of Sciences of the United States of America*. 2024; 121: e2318619121. <https://doi.org/10.1073/pnas.2318619121>.
- [98] Schwärzler J, Grabherr F, Grander C, Adolph TE, Tilg H. The pathophysiology of MASLD: an immunometabolic perspective. *Expert Review of Clinical Immunology*. 2024; 20: 375–386. <https://doi.org/10.1080/1744666X.2023.2294046>.
- [99] Stefan N, Lonardo A, Targher G. Role of steatotic liver disease in prediction and prevention of cardiometabolic diseases. *Nature Reviews. Gastroenterology & Hepatology*. 2024; 21: 136–137. <https://doi.org/10.1038/s41575-023-00880-2>.
- [100] Dongiovanni P, Paolini E, Corsini A, Sirtori CR, Ruscica M. Nonalcoholic fatty liver disease or metabolic dysfunction-associated fatty liver disease diagnoses and cardiovascular diseases: From epidemiology to drug approaches. *European Journal of Clinical Investigation*. 2021; 51: e13519. <https://doi.org/10.1111/eci.13519>.
- [101] Ismaiel A, Dumitrascu DL. Genetic predisposition in metabolic-dysfunction-associated fatty liver disease and cardiovascular outcomes-Systematic review. *European Journal of Clinical Investigation*. 2020; 50: e13331. <https://doi.org/10.1111/eci.13331>.
- [102] Ábel T, Benczúr B, Csobod ÉC. Sex differences in pathogenesis and treatment of dyslipidemia in patients with type 2 diabetes and steatotic liver disease. *Frontiers in Medicine*. 2024; 11: 1458025. <https://doi.org/10.3389/fmed.2024.1458025>.
- [103] Sandireddy R, Sakthivel S, Gupta P, Behari J, Tripathi M, Singh BK. Systemic impacts of metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH) on heart, muscle, and kidney related diseases. *Frontiers in Cell and Developmental Biology*. 2024; 12: 1433857. <https://doi.org/10.3389/fc.ell.2024.1433857>.
- [104] Oh J, Kim BK, Yoon JH, Lee HH, Park H, Lee J, *et al.* Metabolic Dysfunction-Associated Steatotic Liver Disease Is Associated with Increased Risk of Kidney Cancer: A Nationwide Study. *Cancers*. 2024; 16: 3161. <https://doi.org/10.3390/cancers16183161>.
- [105] Targher G, Byrne CD, Tilg H. MASLD: a systemic metabolic disorder with cardiovascular and

- malignant complications. *Gut*. 2024; 73: 691–702. <https://doi.org/10.1136/gutjnl-2023-330595>.
- [106] D'Elia JA, Weinrauch LA. Lipid Toxicity in the Cardiovascular-Kidney-Metabolic Syndrome (CKMS). *Biomedicines*. 2024; 12: 978. <https://doi.org/10.3390/biomedicines12050978>.
- [107] Reid MV, Fredrickson G, Mashek DG. Mechanisms coupling lipid droplets to MASLD pathophysiology. *Hepatology* (Baltimore, Md.). 2024. (online ahead of print) <https://doi.org/10.1097/HEP.0000000000001141>.
- [108] Sookoian S, Rotman Y, Valenti L. Genetics of Metabolic Dysfunction-associated Steatotic Liver Disease: The State of the Art Update. *Clinical Gastroenterology and Hepatology: the Official Clinical Practice Journal of the American Gastroenterological Association*. 2024; 22: 2177–2187.e3. <https://doi.org/10.1016/j.cgh.2024.05.052>.
- [109] Pingitore P, Romeo S. The role of PNPLA3 in health and disease. *Biochimica et Biophysica Acta. Molecular and Cell Biology of Lipids*. 2019; 1864: 900–906. <https://doi.org/10.1016/j.bbalip.2018.06.018>.
- [110] Seko Y, Yamaguchi K, Shima T, Iwaki M, Takahashi H, Kawanaka M, *et al*. The greater impact of PNPLA3 polymorphism on liver-related events in Japanese non-alcoholic fatty liver disease patients: A multicentre cohort study. *Liver International*. 2023; 43: 2210–2219. <https://doi.org/10.1111/liv.15678>.
- [111] Wang Y, Kory N, BasuRay S, Cohen JC, Hobbs HH. PNPLA3, CGI-58, and Inhibition of Hepatic Triglyceride Hydrolysis in Mice. *Hepatology* (Baltimore, Md.). 2019; 69: 2427–2441. <https://doi.org/10.1002/hep.30583>.
- [112] Cherubini A, Ostadrezza M, Jamialahmadi O, Pelusi S, Rrapaj E, Casirati E, *et al*. Interaction between estrogen receptor- α and PNPLA3 p.I148M variant drives fatty liver disease susceptibility in women. *Nature Medicine*. 2023; 29: 2643–2655. <https://doi.org/10.1038/s41591-023-02553-8>.
- [113] Bruschi FV, Tardelli M, Einwallner E, Claudel T, Trauner M. PNPLA3 I148M Up-Regulates Hedgehog and Yap Signaling in Human Hepatic Stellate Cells. *International Journal of Molecular Sciences*. 2020; 21: 8711. <https://doi.org/10.3390/ijms21228711>.
- [114] Gou Y, Wang L, Zhao J, Xu X, Xu H, Xie F, *et al*. PNPLA3-I148M Variant Promotes the Progression of Liver Fibrosis by Inducing Mitochondrial Dysfunction. *International Journal of Molecular Sciences*. 2023; 24: 9681. <https://doi.org/10.3390/ijms24119681>.
- [115] Sherman DJ, Liu L, Mamrosh JL, Xie J, Ferbas J, Lomenick B, *et al*. The fatty liver disease-causing protein PNPLA3-I148M alters lipid droplet-Golgi dynamics. *Proceedings of the National Academy of Sciences of the United States of America*. 2024; 121: e2318619121. <https://doi.org/10.1073/pnas.2318619121>.
- [116] Wang TY, Wang RF, Bu ZY, Targher G, Byrne CD, Sun DQ, *et al*. Association of metabolic dysfunction-associated fatty liver disease with kidney disease. *Nature Reviews. Nephrology*. 2022; 18: 259–268. <https://doi.org/10.1038/s41581-021-00519-y>.
- [117] Romeo S, Kozlitina J, Xing C, Pertsemlidis A, Cox D, Pennacchio LA, *et al*. Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. *Nature Genetics*. 2008; 40: 1461–1465. <https://doi.org/10.1038/ng.257>.
- [118] Mantovani A, Taliento A, Zusi C, Baselli G, Prati D, Granata S, *et al*. PNPLA3 I148M gene variant and chronic kidney disease in type 2 diabetic patients with NAFLD: Clinical and experimental findings. *Liver International*. 2020; 40: 1130–1141. <https://doi.org/10.1111/liv.14419>.
- [119] Castanho Martins M, Dixon ED, Lupo G, Claudel T, Trauner M, Rombouts K. Role of PNPLA3 in Hepatic Stellate Cells and Hepatic Cellular Crosstalk. *Liver International*. 2024. (online ahead of print) <https://doi.org/10.1111/liv.16117>.
- [120] Bilson J, Mantovani A, Byrne CD, Targher G. Steatotic liver disease, MASLD and risk of chronic kidney disease. *Diabetes & Metabolism*. 2024; 50: 101506. <https://doi.org/10.1016/j.diabet.2023.101506>.
- [121] Posadas-Sánchez R, López-Urbe ÁR, Posadas-Romero C, Pérez-Hernández N, Rodríguez-Pérez JM, Ocampo-Arcos WA, *et al*. Association of the I148M/PNPLA3 (rs738409) polymorphism with premature coronary artery disease, fatty liver, and insulin resistance in type 2 diabetic patients and healthy controls. The GEA study. *Immunobiology*. 2017; 222: 960–966. <https://doi.org/10.1016/j.imbio.2016.08.008>.
- [122] Zhang G, Jiang W, He F, Fu J, Xu X, Luo X, *et al*. LDL-C and TC mediate the risk of PNPLA3 inhibition on cardiovascular diseases. *The Journal of Clinical Endocrinology and Metabolism*. 2024; dgae264. <https://doi.org/10.1210/clinem/dgae264>.
- [123] Cobbina E, Akhlaghi F. Non-alcoholic fatty liver disease (NAFLD) - pathogenesis, classification, and effect on drug metabolizing enzymes and transporters. *Drug Metabolism Reviews*. 2017; 49: 197–211. <https://doi.org/10.1080/03602532.2017.1293683>.
- [124] Liu J, Ginsberg HN, Reyes-Soffer G. Basic and translational evidence supporting the role of TM6SF2 in VLDL metabolism. *Current Opinion in Lipidology*. 2024; 35: 157–161. <https://doi.org/10.1097/MOL.0000000000000930>.
- [125] Jiang X, Qian H, Ding WX. New Glance at the Role of TM6SF2 in Lipid Metabolism and Liver Cancer. *Hepatology* (Baltimore, Md.). 2021; 74: 1141–1144. <https://doi.org/10.1002/hep.31851>.
- [126] Pirola CJ, Sookoian S. The dual and opposite role of the TM6SF2-rs58542926 variant in protecting against cardiovascular disease and conferring risk for nonalcoholic fatty liver: A meta-analysis. *Hepatology* (Baltimore, Md.). 2015; 62: 1742–1756. <https://doi.org/10.1002/hep.28142>.
- [127] Wu JT, Liu SS, Xie XJ, Liu Q, Xin YN, Xuan SY. Independent and joint correlation of PNPLA3 I148M and TM6SF2 E167K variants with the risk of coronary heart disease in patients with non-alcoholic fatty liver disease. *Lipids in Health and Disease*. 2020; 19: 29. <https://doi.org/10.1186/s12944-020-01207-9>.
- [128] Byrne CD, Targher G. Non-alcoholic fatty liver disease-related risk of cardiovascular disease and other cardiac complications. *Diabetes, Obesity & Metabolism*. 2022; 24 Suppl 2: 28–43. <https://doi.org/10.1111/dom.14484>.
- [129] Koo BK, An JN, Joo SK, Kim D, Lee S, Bae JM, *et al*. Association Between a Polymorphism in MBOAT7 and Chronic Kidney Disease in Patients With Biopsy-Confirmed Nonalcoholic Fatty Liver Disease. *Clinical Gastroenterology and Hepatology: the Official Clinical Practice Journal of the American Gastroenterological Association*. 2020; 18: 2837–2839.e2. <https://doi.org/10.1016/j.cgh.2019.09.017>.
- [130] Ni W, Lu Y, Wang W. Exploring the interconnected between type 2 diabetes mellitus and nonalcoholic fatty liver disease: Genetic correlation and Mendelian randomization analysis. *Medicine*. 2024; 103: e38008. <https://doi.org/10.1097/MD.00000000000038008>.
- [131] Mancina RM, Dongiovanni P, Petta S, Pingitore P, Meroni M, Rametta R, *et al*. The MBOAT7-TMC4 Variant rs641738 Increases Risk of Nonalcoholic Fatty Liver Disease in Individuals of European Descent. *Gastroenterology*. 2016; 150: 1219–1230.e6. <https://doi.org/10.1053/j.gastro.2016.01.032>.
- [132] Harshfield EL, Fauman EB, Stacey D, Paul DS, Ziemek D, Ong RMY, *et al*. Genome-wide analysis of blood lipid metabolites in over 5000 South Asians reveals biological insights at cardiometabolic disease loci. *BMC Medicine*. 2021; 19: 232. <https://doi.org/10.1186/s12916-021-02087-1>.
- [133] Xiao L, Li Y, Hong C, Ma P, Zhu H, Cui H, *et al*. Polygenic risk score of metabolic dysfunction-associated steatotic liver disease amplifies the health impact on severe liver disease and metabolism-related outcomes. *Journal of Translational Medicine*. 2024; 22: 650. <https://doi.org/10.1186/>

s12967-024-05478-z.

- [134] Yeh KH, Hsu LA, Teng MS, Wu S, Chou HH, Ko YL. Pleiotropic Effects of Common and Rare *GCKR* Exonic Mutations on Cardiometabolic Traits. *Genes*. 2022; 13: 491. <https://doi.org/10.3390/genes13030491>.
- [135] Hishida A, Takashima N, Turin TC, Kawai S, Wakai K, Hamajima N, *et al.* GCK, GCKR polymorphisms and risk of chronic kidney disease in Japanese individuals: data from the J-MICC Study. *Journal of Nephrology*. 2014; 27: 143–149. <https://doi.org/10.1007/s40620-013-0025-0>.
- [136] Ma Y, Belyaeva OV, Brown PM, Fujita K, Valles K, Karki S, *et al.* 17-Beta Hydroxysteroid Dehydrogenase 13 Is a Hepatic Retinol Dehydrogenase Associated With Histological Features of Nonalcoholic Fatty Liver Disease. *Hepatology* (Baltimore, Md.). 2019; 69: 1504–1519. <https://doi.org/10.1002/hep.30350>.
- [137] Abul-Husn NS, Cheng X, Li AH, Xin Y, Schurmann C, Stevis P, *et al.* A Protein-Truncating HSD17B13 Variant and Protection from Chronic Liver Disease. *The New England Journal of Medicine*. 2018; 378: 1096–1106. <https://doi.org/10.1056/NEJMoa1712191>.
- [138] Di Sessa A, Umano GR, Cirillo G, Marzuillo P, Arienzo MR, Pedullà M, *et al.* The rs72613567: TA Variant in the Hydroxysteroid 17-beta Dehydrogenase 13 Gene Reduces Liver Damage in Obese Children. *Journal of Pediatric Gastroenterology and Nutrition*. 2020; 70: 371–374. <https://doi.org/10.1097/MPG.0000000000002573>.
- [139] Zhang H, Chang J, Dai Z, Wang Q, Qiao R, Huang Y, *et al.* Expression and localization of HSD17B13 along mouse urinary tract. *American Journal of Physiology. Renal Physiology*. 2024; 327: F146–F157. <https://doi.org/10.1152/ajprenal.00069.2024>.
- [140] Smiriglia A, Lorito N, Serra M, Perra A, Morandi A, Kowalik MA. Sex difference in liver diseases: How preclinical models help to dissect the sex-related mechanisms sustaining NAFLD and hepatocellular carcinoma. *iScience*. 2023; 26: 108363. <https://doi.org/10.1016/j.isci.2023.108363>.
- [141] Cherubini A, Rosso C, Della Torre S. Sex-specific effects of PNPLA3 I148M. *Liver International*. 2024. (online ahead of print) <https://doi.org/10.1111/liv.16088>.
- [142] Petta S, Armandi A, Bugianesi E. Impact of PNPLA3 I148M on Clinical Outcomes in Patients With MASLD. *Liver International*. 2024. (online ahead of print) <https://doi.org/10.1111/liv.16133>.
- [143] Tsuei DJ, Lee PH, Peng HY, Lu HL, Su DS, Jeng YM, *et al.* Male germ cell-specific RNA binding protein RBMY: a new oncogene explaining male predominance in liver cancer. *PloS One*. 2011; 6: e26948. <https://doi.org/10.1371/journal.pone.0026948>.
- [144] García-Calzón S, Perflyev A, de Mello VD, Pihlajamäki J, Ling C. Sex Differences in the Methylome and Transcriptome of the Human Liver and Circulating HDL-Cholesterol Levels. *The Journal of Clinical Endocrinology and Metabolism*. 2018; 103: 4395–4408. <https://doi.org/10.1210/jc.2018-00423>.
- [145] Alemany M. Estrogens and the regulation of glucose metabolism. *World Journal of Diabetes*. 2021; 12: 1622–1654. <https://doi.org/10.4239/wjdv.12.i10.1622>.
- [146] Zhu J, Zhang L, Ji M, Jin B, Shu J. Elevated adipose differentiation-related protein level in ovariectomized mice correlates with tissue-specific regulation of estrogen. *The Journal of Obstetrics and Gynaecology Research*. 2023; 49: 1173–1179. <https://doi.org/10.1111/jog.15565>.
- [147] Juszczak F, Pierre L, Decamonde M, Jadot I, Martin B, Botton O, *et al.* Sex differences in obesity-induced renal lipid accumulation revealed by lipidomics: a role of adiponectin/AMPK axis. *Biology of Sex Differences*. 2023; 14: 63. <https://doi.org/10.1186/s13293-023-00543-6>.
- [148] Akter MH, Yamaguchi T, Hirose F, Osumi T. Perilipin, a critical regulator of fat storage and breakdown, is a target gene of estrogen receptor-related receptor alpha. *Biochemical and Biophysical Research Communications*. 2008; 368: 563–568. <https://doi.org/10.1016/j.bbrc.2008.01.102>.
- [149] Burra P, Bizzaro D, Gonta A, Shalaby S, Gambato M, Morelli MC, *et al.* Clinical impact of sexual dimorphism in non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH). *Liver International*. 2021; 41: 1713–1733. <https://doi.org/10.1111/liv.14943>.
- [150] Wu J, Yao XY, Shi RX, Liu SF, Wang XY. A potential link between polycystic ovary syndrome and non-alcoholic fatty liver disease: an update meta-analysis. *Reproductive Health*. 2018; 15: 77. <https://doi.org/10.1186/s12978-018-0519-2>.
- [151] Jaruvongvanich V, Sanguankeo A, Rianguwat T, Upala S. Testosterone, Sex Hormone-Binding Globulin and Nonalcoholic Fatty Liver Disease: a Systematic Review and Meta-Analysis. *Annals of Hepatology*. 2017; 16: 382–394. <https://doi.org/10.5604/16652681.1235481>.
- [152] Mitrofanova A, Merscher S, Fornoni A. Kidney lipid dysmetabolism and lipid droplet accumulation in chronic kidney disease. *Nature Reviews. Nephrology*. 2023; 19: 629–645. <https://doi.org/10.1038/s41581-023-00741-w>.
- [153] Hammoud SH, AlZaim I, Al-Dhaheri Y, Eid AH, El-Yazbi AF. Perirenal Adipose Tissue Inflammation: Novel Insights Linking Metabolic Dysfunction to Renal Diseases. *Frontiers in Endocrinology*. 2021; 12: 707126. <https://doi.org/10.3389/fendo.2021.707126>.
- [154] Jiang Z, Wang Y, Zhao X, Cui H, Han M, Ren X, *et al.* Obesity and chronic kidney disease. *American Journal of Physiology. Endocrinology and Metabolism*. 2023; 324: E24–E41. <https://doi.org/10.1152/ajpendo.00179.2022>.
- [155] D'Marco L, Salazar J, Cortez M, Salazar M, Wetzel M, Lima-Martínez M, *et al.* Perirenal fat thickness is associated with metabolic risk factors in patients with chronic kidney disease. *Kidney Research and Clinical Practice*. 2019; 38: 365–372. <https://doi.org/10.23876/j.krcp.18.0155>.
- [156] Qi XY, Qu SL, Xiong WH, Rom O, Chang L, Jiang ZS. Perivascular adipose tissue (PVAT) in atherosclerosis: a double-edged sword. *Cardiovascular Diabetology*. 2018; 17: 134. <https://doi.org/10.1186/s12933-018-0777-x>.
- [157] Carullo N, Zicarelli M, Michael A, Faga T, Battaglia Y, Pisani A, *et al.* Childhood Obesity: Insight into Kidney Involvement. *International Journal of Molecular Sciences*. 2023; 24: 17400. <https://doi.org/10.3390/ijms242417400>.
- [158] Meléndez-Salcido CG, Ramírez-Emiliano J, Pérez-Vázquez V. Hypercaloric Diet Promotes Metabolic Disorders and Impaired Kidney Function. *Current Pharmaceutical Design*. 2022; 28: 3127–3139. <https://doi.org/10.2174/1381612829666221020162955>.
- [159] Loneker AE, Alisafaei F, Kant A, Li D, Janmey PA, Shenoy VB, *et al.* Lipid droplets are intracellular mechanical stressors that impair hepatocyte function. *Proceedings of the National Academy of Sciences of the United States of America*. 2023; 120: e221681120. <https://doi.org/10.1073/pnas.221681120>.
- [160] Rampanelli E, Ochodnický P, Vissers JP, Butter LM, Claessen N, Calcagni A, *et al.* Excessive dietary lipid intake provokes an acquired form of lysosomal lipid storage disease in the kidney. *The Journal of Pathology*. 2018; 246: 470–484. <https://doi.org/10.1002/path.5150>.
- [161] Gurumani M, Mallela SK, Varona J, Merscher S, Fornoni A, Al-Ali H. A Robust Phenotypic Screening Assay Utilizing Human Podocytes to Identify Agents that Modulate Lipid Droplets. *Methods in Molecular Biology* (Clifton, N.J.). 2023; 2625: 163–174. https://doi.org/10.1007/978-1-0716-2966-6_15.
- [162] Mallela SK, Patel DM, Ducasa GM, Merscher S, Fornoni A, Al-Ali H. Detection and Quantification of Lipid Droplets in Differentiated Human Podocytes. *Methods in Molecular Biology* (Clifton, N.J.). 2019; 1996: 199–206. https://doi.org/10.1007/978-1-4939-9488-5_17.

- [163] Martínez-García C, Izquierdo-Lahuerta A, Vivas Y, Velasco I, Yeo TK, Chen S, *et al.* Renal Lipotoxicity-Associated Inflammation and Insulin Resistance Affects Actin Cytoskeleton Organization in Podocytes. *PloS One*. 2015; 10: e0142291. <https://doi.org/10.1371/journal.pone.0142291>.
- [164] Ma Y, Shi M, Wang Y, Liu J. PPAR γ and Its Agonists in Chronic Kidney Disease. *International Journal of Nephrology*. 2020; 2020: 2917474. <https://doi.org/10.1155/2020/2917474>.
- [165] Krukowski H, Valkenburg S, Madella AM, Garssen J, van Bergenhenegouwen J, Overbeek SA, *et al.* Gut microbiome studies in CKD: opportunities, pitfalls and therapeutic potential. *Nature Reviews. Nephrology*. 2023; 19: 87–101. <https://doi.org/10.1038/s41581-022-00647-z>.
- [166] Banke NH, Lewandowski ED. Impaired cytosolic NADH shuttling and elevated UCP3 contribute to inefficient citric acid cycle flux support of postischemic cardiac work in diabetic hearts. *Journal of Molecular and Cellular Cardiology*. 2015; 79: 13–20. <https://doi.org/10.1016/j.yjmcc.2014.10.015>.
- [167] Lahey R, Wang X, Carley AN, Lewandowski ED. Dietary fat supply to failing hearts determines dynamic lipid signaling for nuclear receptor activation and oxidation of stored triglyceride. *Circulation*. 2014; 130: 1790–1799. <https://doi.org/10.1161/CIRCULATIONAHA.114.011687>.
- [168] Goldberg IJ, Reue K, Abumrad NA, Bickel PE, Cohen S, Fisher EA, *et al.* Deciphering the Role of Lipid Droplets in Cardiovascular Disease: A Report From the 2017 National Heart, Lung, and Blood Institute Workshop. *Circulation*. 2018; 138: 305–315. <https://doi.org/10.1161/CIRCULATIONAHA.118.033704>.
- [169] Drevigne C, Dalen KT, Mannila MN, Täng MS, Ståhlman M, Klewing M, *et al.* Perilipin 5 is protective in the ischemic heart. *International Journal of Cardiology*. 2016; 219: 446–454. <https://doi.org/10.1016/j.ijcard.2016.06.037>.
- [170] Holzem KM, Vinnakota KC, Ravikumar VK, Madden EJ, Ewald GA, Dikranian K, *et al.* Mitochondrial structure and function are not different between nonfailing donor and end-stage failing human hearts. *FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology*. 2016; 30: 2698–2707. <https://doi.org/10.1096/fj.201500118R>.
- [171] Kuramoto K, Okamura T, Yamaguchi T, Nakamura TY, Wakabayashi S, Morinaga H, *et al.* Perilipin 5, a lipid droplet-binding protein, protects heart from oxidative burden by sequestering fatty acid from excessive oxidation. *The Journal of Biological Chemistry*. 2012; 287: 23852–23863. <https://doi.org/10.1074/jbc.M111.328708>.
- [172] Wang H, Sreenivasan U, Gong DW, O'Connell KA, Dabkowski ER, Hecker PA, *et al.* Cardiomyocyte-specific perilipin 5 overexpression leads to myocardial steatosis and modest cardiac dysfunction. *Journal of Lipid Research*. 2013; 54: 953–965. <https://doi.org/10.1194/jlr.M032466>.
- [173] Carpentier AC. Abnormal Myocardial Dietary Fatty Acid Metabolism and Diabetic Cardiomyopathy. *The Canadian Journal of Cardiology*. 2018; 34: 605–614. <https://doi.org/10.1016/j.cjca.2017.12.029>.
- [174] Han L, Huang D, Wu S, Liu S, Wang C, Sheng Y, *et al.* Lipid droplet-associated lncRNA LIPTER preserves cardiac lipid metabolism. *Nature Cell Biology*. 2023; 25: 1033–1046. <https://doi.org/10.1038/s41556-023-01162-4>.
- [175] Vengrenyuk Y, Nishi H, Long X, Ouimet M, Savji N, Martinez FO, *et al.* Cholesterol loading reprograms the microRNA-143/145-myocardin axis to convert aortic smooth muscle cells to a dysfunctional macrophage-like phenotype. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2015; 35: 535–546. <https://doi.org/10.1161/ATVBAHA.114.304029>.
- [176] Allahverdian S, Chehroudi AC, McManus BM, Abraham T, Francis GA. Contribution of intimal smooth muscle cells to cholesterol accumulation and macrophage-like cells in human atherosclerosis. *Circulation*. 2014; 129: 1551–1559. <https://doi.org/10.1161/CIRCULATIONAHA.113.005015>.
- [177] Lee JA, Hall B, Allsop J, Alqarni R, Allen SP. Lipid metabolism in astrocytic structure and function. *Seminars in Cell & Developmental Biology*. 2021; 112: 123–136. <https://doi.org/10.1016/j.semdb.2020.07.017>.
- [178] Hogenboom R, Kalsbeek MJ, Korpel NL, de Goede P, Koenen M, Buijs RM, *et al.* Loss of arginine vasopressin- and vasoactive intestinal polypeptide-containing neurons and glial cells in the suprachiasmatic nucleus of individuals with type 2 diabetes. *Diabetologia*. 2019; 62: 2088–2093. <https://doi.org/10.1007/s00125-019-4953-7>.
- [179] Folick A, Koliwad SK, Valdearcos M. Microglial Lipid Biology in the Hypothalamic Regulation of Metabolic Homeostasis. *Frontiers in Endocrinology*. 2021; 12: 668396. <https://doi.org/10.3389/fendo.2021.668396>.
- [180] Wang X, Li H. Chronic high-fat diet induces overeating and impairs synaptic transmission in feeding-related brain regions. *Frontiers in Molecular Neuroscience*. 2022; 15: 1019446. <https://doi.org/10.3389/fnmol.2022.1019446>.
- [181] Bolborea M, Langlet F. What is the physiological role of hypothalamic tanycytes in metabolism? *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology*. 2021; 320: R994–R1003. <https://doi.org/10.1152/ajpregu.00296.2020>.
- [182] Hirsch-Reinshagen V, Donkin J, Stukas S, Chan J, Wilkinson A, Fan J, *et al.* LCAT synthesized by primary astrocytes esterifies cholesterol on glia-derived lipoproteins. *Journal of Lipid Research*. 2009; 50: 885–893. <https://doi.org/10.1194/jlr.M800584-JLR200>.
- [183] Liu D, Wang T, Zhao X, Chen J, Yang T, Shen Y, *et al.* Saturated fatty acids stimulate cytokine production in tanycytes via the PP2Ac-dependent signaling pathway. *Journal of Cerebral Blood Flow and Metabolism: Official Journal of the International Society of Cerebral Blood Flow and Metabolism*. 2024; 44: 985–999. <https://doi.org/10.1177/0271678X231219115>.
- [184] Wang H, Eckel RH. What are lipoproteins doing in the brain? *Trends in Endocrinology and Metabolism: TEM*. 2014; 25: 8–14. <https://doi.org/10.1016/j.tem.2013.10.003>.
- [185] Jackson CL, Walch L, Verbavatz JM. Lipids and Their Trafficking: An Integral Part of Cellular Organization. *Developmental Cell*. 2016; 39: 139–153. <https://doi.org/10.1016/j.devcel.2016.09.030>.
- [186] Zhou YD. Glial Regulation of Energy Metabolism. *Advances in Experimental Medicine and Biology*. 2018; 1090: 105–121. https://doi.org/10.1007/978-981-13-1286-1_6.
- [187] Trommsdorff M, Gotthardt M, Hiesberger T, Shelton J, Stockinger W, Nimpf J, *et al.* Reeler/Disabled-like disruption of neuronal migration in knockout mice lacking the VLDL receptor and ApoE receptor 2. *Cell*. 1999; 97: 689–701. [https://doi.org/10.1016/S0092-8674\(00\)80782-5](https://doi.org/10.1016/S0092-8674(00)80782-5).
- [188] Gao Y, Layritz C, Legutko B, Eichmann TO, Laperrousaz E, Moullé VS, *et al.* Disruption of Lipid Uptake in Astroglia Exacerbates Diet-Induced Obesity. *Diabetes*. 2017; 66: 2555–2563. <https://doi.org/10.2337/db16-1278>.
- [189] Laperrousaz E, Moullé VS, Denis RG, Kassis N, Berland C, Colsch B, *et al.* Lipoprotein lipase in hypothalamus is a key regulator of body weight gain and glucose homeostasis in mice. *Diabetologia*. 2017; 60: 1314–1324. <https://doi.org/10.1007/s00125-017-4282-7>.
- [190] Wang H, Wang Y, Taussig MD, Eckel RH. Sex differences in obesity development in pair-fed neuronal lipoprotein lipase deficient mice. *Molecular Metabolism*. 2016; 5: 1025–1032. <https://doi.org/10.1016/j.molmet.2016.05.013>.
- [191] Cleland NRW, Bruce KD. Fatty acid sensing in the brain: The role of glial-neuronal metabolic crosstalk and horizontal lipid flux. *Biochimie*. 2024; 223: 166–178. <https://doi.org/10.1016/j.biochi.2022.08.012>.
- [192] Rojas-Carranza CA, Bustos-Cruz RH, Pino-Pinzon CJ, Ariza-

- Marquez YV, Gomez-Bello RM, Canadas-Garre M. Diabetes-Related Neurological Implications and Pharmacogenomics. *Current Pharmaceutical Design*. 2018; 24: 1695–1710. <https://doi.org/10.2174/1381612823666170317165350>.
- [193] Li Q, Zhao Y, Guo H, Li Q, Yan C, Li Y, *et al.* Impaired lipophagy induced-microglial lipid droplets accumulation contributes to the buildup of TREM1 in diabetes-associated cognitive impairment. *Autophagy*. 2023; 19: 2639–2656. <https://doi.org/10.1080/15548627.2023.2213984>.
- [194] Subhramanyam CS, Wang C, Hu Q, Dheen ST. Microglia-mediated neuroinflammation in neurodegenerative diseases. *Seminars in Cell & Developmental Biology*. 2019; 94: 112–120. <https://doi.org/10.1016/j.semcdb.2019.05.004>.
- [195] Hickman S, Izzy S, Sen P, Morsett L, El Khoury J. Microglia in neurodegeneration. *Nature Neuroscience*. 2018; 21: 1359–1369. <https://doi.org/10.1038/s41593-018-0242-x>.
- [196] Zhang K, Kaufman RJ. From endoplasmic-reticulum stress to the inflammatory response. *Nature*. 2008; 454: 455–462. <https://doi.org/10.1038/nature07203>.
- [197] Valdearcos M, Robblee MM, Benjamin DI, Nomura DK, Xu AW, Koliwad SK. Microglia dictate the impact of saturated fat consumption on hypothalamic inflammation and neuronal function. *Cell Reports*. 2014; 9: 2124–2138. <https://doi.org/10.1016/j.celrep.2014.11.018>.
- [198] Shimabukuro MK, Langhi LGP, Cordeiro I, Brito JM, Batista CMD, Mattson MP, *et al.* Lipid-laden cells differentially distributed in the aging brain are functionally active and correspond to distinct phenotypes. *Scientific Reports*. 2016; 6: 23795. <https://doi.org/10.1038/srep23795>.
- [199] Byrns CN, Perlegos AE, Miller KN, Jin Z, Carranza FR, Manchandra P, *et al.* Senescent glia link mitochondrial dysfunction and lipid accumulation. *Nature*. 2024; 630: 475–483. <https://doi.org/10.1038/s41586-024-07516-8>.
- [200] Lau V, Ramer L, Tremblay ME. An aging, pathology burden, and glial senescence build-up hypothesis for late onset Alzheimer's disease. *Nature Communications*. 2023; 14: 1670. <https://doi.org/10.1038/s41467-023-37304-3>.
- [201] Reyes JF, Devarajan M, Cai D, Mashek DG. Senescent glia-bridging neuronal mitochondrial dysfunction and lipid accumulation in aging. *Life Metabolism*. 2024; 3: loae031. <https://doi.org/10.1093/lifemeta/loae031>.
- [202] Islimye E, Girard V, Gould AP. Functions of Stress-Induced Lipid Droplets in the Nervous System. *Frontiers in Cell and Developmental Biology*. 2022; 10: 863907. <https://doi.org/10.3389/fcell.2022.863907>.
- [203] Haney MS, Pálovics R, Munson CN, Long C, Johansson PK, Yip O, *et al.* APOE4/4 is linked to damaging lipid droplets in Alzheimer's disease microglia. *Nature*. 2024; 628: 154–161. <https://doi.org/10.1038/s41586-024-07185-7>.
- [204] Ogrodnik M, Zhu Y, Langhi LGP, Tchkonian T, Krüger P, Fielder E, *et al.* Obesity-Induced Cellular Senescence Drives Anxiety and Impairs Neurogenesis. *Cell Metabolism*. 2019; 29: 1233. <https://doi.org/10.1016/j.cmet.2019.01.013>.
- [205] Goodman T, Hajihosseini MK. Hypothalamic tanycytes-masters and servants of metabolic, neuroendocrine, and neurogenic functions. *Frontiers in Neuroscience*. 2015; 9: 387. <https://doi.org/10.3389/fnins.2015.00387>.
- [206] Elizondo-Vega RJ, Recabal A, Oyarce K. Nutrient Sensing by Hypothalamic Tanycytes. *Frontiers in Endocrinology*. 2019; 10: 244. <https://doi.org/10.3389/fendo.2019.00244>.
- [207] Langlet F. Tanycyte Gene Expression Dynamics in the Regulation of Energy Homeostasis. *Frontiers in Endocrinology*. 2019; 10: 286. <https://doi.org/10.3389/fendo.2019.00286>.
- [208] Maya-Monteiro CM, Corrêa-da-Silva F, Hofmann SS, Hesselink MKC, la Fleur SE, Yi CX. Lipid Droplets Accumulate in the Hypothalamus of Mice and Humans with and without Metabolic Diseases. *Neuroendocrinology*. 2021; 111: 263–272. <https://doi.org/10.1159/000508735>.
- [209] Hofmann K, Lamertz C, Piotrowitz K, Offermann N, But D, Scheller A, *et al.* Tanycytes and a differential fatty acid metabolism in the hypothalamus. *Glia*. 2017; 65: 231–249. <https://doi.org/10.1002/glia.23088>.
- [210] Brunner M, Lopez-Rodriguez D, Estrada-Meza J, Dali R, Rohrbach A, Deglise T, *et al.* Fasting induces metabolic switches and spatial redistributions of lipid processing and neuronal interactions in tanycytes. *Nature Communications*. 2024; 15: 6604. <https://doi.org/10.1038/s41467-024-50913-w>.
- [211] Geller S, Arribat Y, Netzahualcoyotzi C, Lagarrigue S, Carneiro L, Zhang L, *et al.* Tanycytes Regulate Lipid Homeostasis by Sensing Free Fatty Acids and Signaling to Key Hypothalamic Neuronal Populations via FGF21 Secretion. *Cell Metabolism*. 2019; 30: 833–844.e7. <https://doi.org/10.1016/j.cmet.2019.08.004>.
- [212] Ogrodnik M, Zhu Y, Langhi LGP, Tchkonian T, Krüger P, Fielder E, *et al.* Obesity-Induced Cellular Senescence Drives Anxiety and Impairs Neurogenesis. *Cell Metabolism*. 2019; 29: 1061–1077.e8. <https://doi.org/10.1016/j.cmet.2018.12.008>.
- [213] Hamilton LK, Fernandes KJL. Neural stem cells and adult brain fatty acid metabolism: Lessons from the 3xTg model of Alzheimer's disease. *Biology of the Cell*. 2018; 110: 6–25. <https://doi.org/10.1111/boc.201700037>.
- [214] Duquenne M, Folgueira C, Bourouh C, Millet M, Silva A, Clasadonte J, *et al.* Leptin brain entry via a tanycytic LepR-EGFR shuttle controls lipid metabolism and pancreas function. *Nature Metabolism*. 2021; 3: 1071–1090. <https://doi.org/10.1038/s42255-021-00432-5>.
- [215] Imbernon M, Saponaro C, Helms HCC, Duquenne M, Fernandois D, Deligia E, *et al.* Tanycytes control hypothalamic liraglutide uptake and its anti-obesity actions. *Cell Metabolism*. 2022; 34: 1054–1063.e7. <https://doi.org/10.1016/j.cmet.2022.06.002>.
- [216] Cristino L, Busetto G, Imperatore R, Ferrandino I, Palomba L, Silvestri C, *et al.* Obesity-driven synaptic remodeling affects endocannabinoid control of orexinergic neurons. *Proceedings of the National Academy of Sciences of the United States of America*. 2013; 110: E2229–E2238. <https://doi.org/10.1073/pnas.1219485110>.
- [217] Xi D, Gandhi N, Lai M, Kublaoui BM. Ablation of Sim1 neurons causes obesity through hyperphagia and reduced energy expenditure. *PloS One*. 2012; 7: e36453. <https://doi.org/10.1371/journal.pone.0036453>.
- [218] Polyzos SA, Kountouras J, Mantzoros CS. Obesity and nonalcoholic fatty liver disease: From pathophysiology to therapeutics. *Metabolism: Clinical and Experimental*. 2019; 92: 82–97. <https://doi.org/10.1016/j.metabol.2018.11.014>.
- [219] Elholm M, Garras A, Neve S, Tornehave D, Lund TB, Skorve J, *et al.* Long-chain acyl-CoA esters and acyl-CoA binding protein are present in the nucleus of rat liver cells. *Journal of Lipid Research*. 2000; 41: 538–545.
- [220] Siddiqi S, Zhelyabovska O, Siddiqi SA. Reticulon 3 regulates very low density lipoprotein secretion by controlling very low density lipoprotein transport vesicle biogenesis. *Canadian Journal of Physiology and Pharmacology*. 2018; 96: 668–675. <https://doi.org/10.1139/cjpp-2018-0077>.
- [221] Olofsson SO, Borén J. Apolipoprotein B secretory regulation by degradation. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2012; 32: 1334–1338. <https://doi.org/10.1161/ATVBAHA.112.251116>.
- [222] Wang H, Nikain C, Fortounas KI, Amengual J, Tufanli O, La Forest M, *et al.* FITM2 deficiency results in ER lipid accumulation, ER stress, and reduced apolipoprotein B lipidation and VLDL triglyceride secretion in vitro and in mouse liver. *Molecular Metabolism*. 2024; 90: 102048.
- [223] Haider A, Wei YC, Lim K, Barbosa AD, Liu CH, Weber U, *et al.* PCYT1A Regulates Phosphatidylcholine Homeostasis from the Inner Nuclear Membrane in Response to Membrane Stored

- Curvature Elastic Stress. *Developmental Cell*. 2018; 45: 481–495.e8. <https://doi.org/10.1016/j.devcel.2018.04.012>.
- [224] Yue L, McPhee MJ, Gonzalez K, Charman M, Lee J, Thompson J, *et al*. Differential dephosphorylation of CTP:phosphocholine cytidyltransferase upon translocation to nuclear membranes and lipid droplets. *Molecular Biology of the Cell*. 2020; 31: 1047–1059. <https://doi.org/10.1091/mbc.E20-01-0014>.
- [225] McPhee M, Lee J, Salsman J, Pinelli M, Di Cara F, Rosen K, *et al*. Nuclear lipid droplets in Caco2 cells originate from nascent precursors and in situ at the nuclear envelope. *Journal of Lipid Research*. 2024; 65: 100540. <https://doi.org/10.1016/j.jlr.2024.100540>.
- [226] Fujimoto T. Nuclear lipid droplets - how are they different from their cytoplasmic siblings? *Journal of Cell Science*. 2022; 135: jcs259253. <https://doi.org/10.1242/jcs.259253>.
- [227] Goulbourne CN, Malhas AN, Vaux DJ. The induction of a nucleoplasmic reticulum by prelamin A accumulation requires CTP:phosphocholine cytidyltransferase- α . *Journal of Cell Science*. 2011; 124: 4253–4266. <https://doi.org/10.1242/jcs.091009>.
- [228] Gehrig K, Cornell RB, Ridgway ND. Expansion of the nucleoplasmic reticulum requires the coordinated activity of lamins and CTP:phosphocholine cytidyltransferase alpha. *Molecular Biology of the Cell*. 2008; 19: 237–247. <https://doi.org/10.1091/mbc.e07-02-0179>.
- [229] Foster J, McPhee M, Yue L, Dellaire G, Pelech S, Ridgway ND. Lipid- and phospho-regulation of CTP:Phosphocholine Cytidyltransferase α association with nuclear lipid droplets. *Molecular Biology of the Cell*. 2024; 35: ar33. <https://doi.org/10.1091/mbc.E23-09-0354>.
- [230] Liu XH, Pang X, Jin L, Pu DY, Wang ZJ, Zhang YG. Exposure to acute waterborne cadmium caused severe damage on lipid metabolism of freshwater fish, revealed by nuclear lipid droplet deposition in hepatocytes of rare minnow. *Aquatic Toxicology* (Amsterdam, Netherlands). 2023; 257: 106433. <https://doi.org/10.1016/j.aquatox.2023.106433>.
- [231] Hu Y, Wang R, Liu J, Wang Y, Dong J. Lipid droplet deposition in the regenerating liver: A promoter, inhibitor, or bystander? *Hepatology Communications*. 2023; 7: e0267. <https://doi.org/10.1097/HC9.0000000000000267>.