Expert Review of Proteomics

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ieru20

Lipid droplets diversity and functions in inflammation and immune response

Filipe S. Pereira-Dutra & Patrícia T. Bozza

To cite this article: Filipe S. Pereira-Dutra & Patrícia T. Bozza (2021) Lipid droplets diversity and functions in inflammation and immune response, Expert Review of Proteomics, 18:9, 809-825, DOI: 10.1080/14789450.2021.1995356

To link to this article: https://doi.org/10.1080/14789450.2021.1995356

Published online: 01 Nov 2021.

EXPERT REVIEW OF PROTEOMICS
2021, VOL. 18, NO. 9, 809–825
https://doi.org/10.1080/14789450.2021.1995356

Taylor & Francis
Taylor & Francis Group

REVIEW

Lipid droplets diversity and functions in inflammation and immune response

Filipe S. Pereira-Dutra and Patrícia T. Bozza

Laboratório de Imunofarmacologia, Instituto Oswaldo Cruz, Fundação Oswaldo Cruz, Rio de Janeiro, Brazil

ABSTRACT

Introduction: Lipid droplets (LDs) are dynamic and evolutionary conserved lipid-enriched organelles composed of a core of neutral lipids surrounded by a monolayer of phospholipids associated with a diverse array of proteins that are cell- and stimulus-regulated. Far beyond being simply a deposit of neutral lipids, accumulating evidence demonstrate that LDs act as spatial and temporal local for lipid and protein compartmentalization and signaling organization.

Areas covered: This review focuses on the progress in our understanding of LD protein diversity and LD functions in the context of cell signaling and immune responses, highlighting the relationship between LD composition with the multiple roles of this organelle in immunometabolism, inflammation and host-response to infection.

Expert opinion: LDs are essential platforms for various cellular processes, including metabolic regulation, cell signaling, and immune responses. The functions of LD in infection and inflammatory disease are associated with the dynamic and complexity of their proteome. Our contemporary view place LDs as critical regulators of different inflammatory and infectious diseases and key markers of leukocyte activation.

ARTICLE HISTORY
Received 3 July 2021
Accepted 15 October 2021

KEYWORDS
Lipid metabolism; inflammation; lipid droplets; organelle proteome; eicosanoids; organelle interaction; immunometabolism

1. Introduction

Lipids droplets (LDs) are cytoplasmic lipid-enriched organelles that can be found virtually in all types of cells, from prokaryotes to multicellular eukaryotes [1,2]. Although LD was one of the first cellular structures described, these organelles were considered passive cytosolic inclusions for more than a century [3,4]. This perception has changed dramatically in the last three decades, where several studies metamorphosed the LDs into multifunction organelles, with crucial functions in cell metabolism, lipid biology, and cell signaling [5–7]. Furthermore, LD biogenesis and accumulation result from the cellular balance between the synthesis and the degradation of lipids, which play a critical role in energy and redox homeostasis [8,9]. LDs' size, number, spatial organization, and functions differ considerably among different cell types and even in individual cells in a population [2,7,8]. The plasticity of LDs is closely related to the diversity of the lipid and protein content of LDs, strongly dependent on the cellular metabolic state [10,11].

In the immuno-inflammatory context, LDs formation is part of metabolic reprogramming in leukocytes [12–14], and a hallmark of the inflammatory process both in the innate and adaptive immune response [15–17]. Moreover, the participation of LDs in infectious disease pathogenesis has been reported for all classes of pathogens, such as viruses, protozoan parasites, bacteria, and fungi [17–19]. Accumulating data demonstrate that different roles of LD in infection and inflammatory disease have been associated with the dynamic and complexity of their proteome in leukocytes, among other cells [20–22]. In this context, LDs act as an important scaffold to cell signaling [23] and metabolic pathways, mainly lipid metabolism [24] and eicosanoid synthesis [25,26]. In addition, several cellular processes associated with LDs are due to these physical interactions with other organelles, a highly regulated process involving several proteins [27,28].

Based on recent advances in LD biology, the focus of this article is to review progress in our understanding of LD protein diversity and functions in the context of inflammation and immunity, highlighting the relationship between LD composition with the multiple roles of this organelle in inflammatory mediator production, immunometabolism and host-pathogen interactions.

2. LD as central player in lipid homeostasis

Structurally, LD is an endoplasmic reticulum (RE)-derived organelle [29], delimited by a monolayer of phospholipid associated with a diverse composition of proteins, which covers a hydrophobic core composed of neutral lipids, mainly triacylglycerol (TAG), diacylglycerol (DAG) and cholesteryl esters (CEs) [2,8,30]. Despite the events that lead to the *de novo* formation of LDs are still not fully understood, the current biogenesis models suggest that LDs buds from the outer leaflet of the ER. Moreover, the biogenesis of LD is triggered by neutral lipid synthesis at ER, the primary site where critical enzymes involved in neutral lipid synthesis are located, such as diacylglycerol O-acyltransferases (DGAT1 and DGAT2) [31,32], and acyl-CoA: cholesterol O-acyltransferases/sterol

CONTACT Patrícia T. Bozza pbozza@ioc.fiocruz.br Laboratório de Imunofarmacologia, Instituto Oswaldo Cruz, Fundação Oswaldo Cruz, Avenida Brasil, 4365, Manguinhos, Rio de Janeiro, RJ CEP 21045-900, Brazil

Article highlights

- LD accumulation is a highly regulated and multiple-step process whose mechanisms and mobilized signaling pathways are dependent on the cell type involved and stimulatory conditions.
- The LD proteome is dynamic and complex, housing numerous proteins. The great protein and lipid diversity inherently determine the functions of LDs observed in different cell types.
- The physical interactions of LDs with other cell compartments allow the exchange of contents and the integration of lipid metabolism.
- The LDs' interaction with other organelles also has to be highlighted as a key process in the host-pathogen interaction, both in pro-host response and pathogens survival and replication.
- In leukocytes and other cells of the immune response, LDs are central organelles in cell signaling, inflammatory mediator production and immunometabolic reprogramming.

O-acyltransferases (ACAT1/SOAT1 and ACAT2/SOAT2) [33–35], responsible for the synthesis of triacylglycerols (TAG) and sterol esters (CE), respectively. Of note, in several situations, LDs remain in intimate interaction and/or with incorporated membranes from ER [36].

LD accumulation is a highly regulated and multiple-step process whose mechanisms and mobilized signaling pathways are dependent on the cell type involved and stimulatory conditions [15,37]. Beyond increasing the synthesis of neutral lipids, the LD biogenesis and accumulation are also reliant on other disturbances of lipid metabolism, such as increased lipid uptake (e.g. low-density lipoprotein receptor -LDLR and CD36), cholesterol efflux, autophagy, and lipid remodeling [11,33,38–41]. In addition to the increase of the lipid content in the cells, the assembly, biogenesis, and stability of LD are also dependent on the participation of LD structural proteins [42,43], the perilipin (Plin) family, consisting of five proteins previously known as the PAT family of proteins, include Plin1, Plin2/ADRP, Plin3/TIP47, Plin4/S3-12, and Plin5/OXPAT/LSDP5 [42–44]. Recent results have been reported that Plin1a and Plin5 were associated with TAG-rich LDs, while Plin1c and

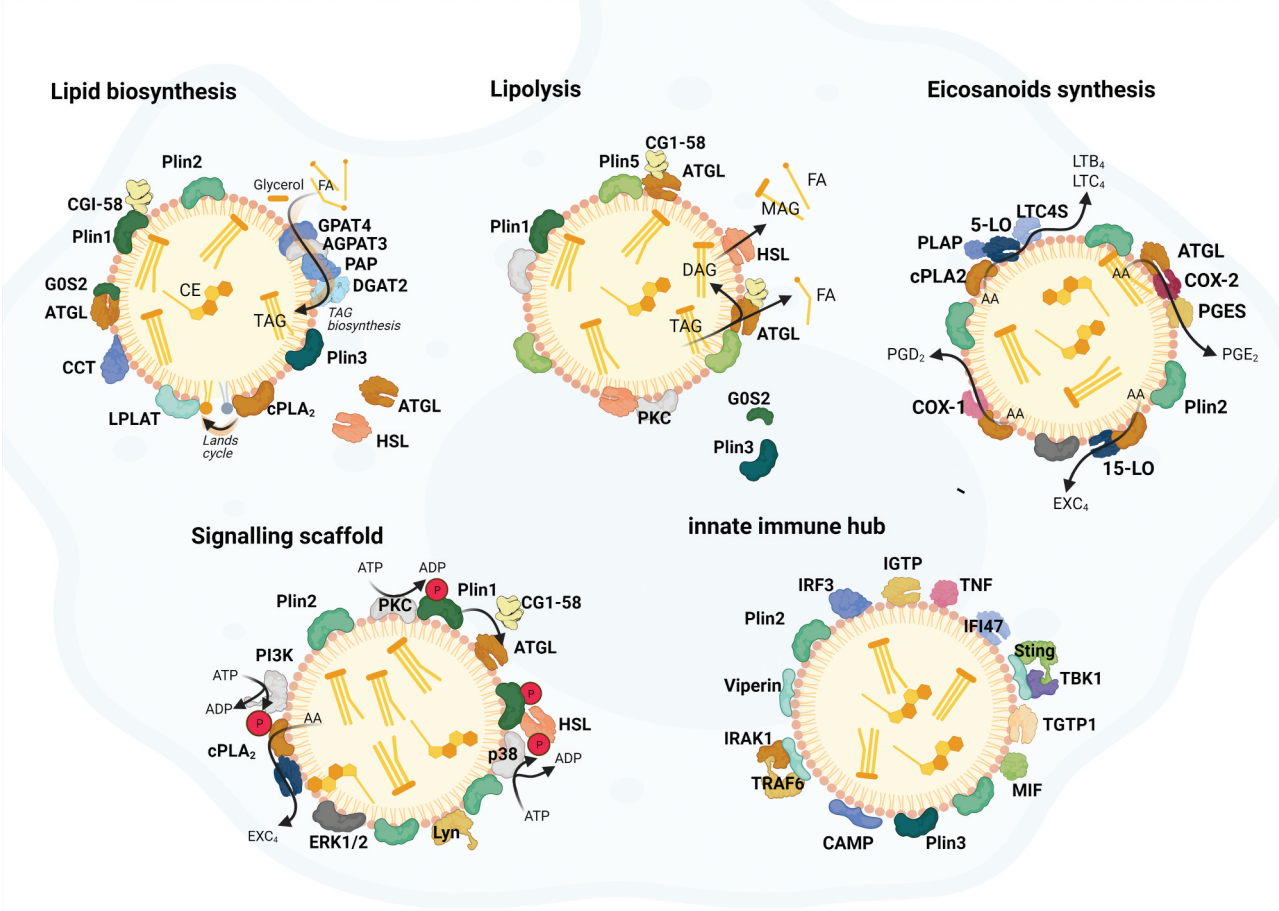

Figure 1. The role of lipid droplets is dependent on their protein composition. the LD proteome is dynamic and complex, housing numerous proteins, which inherently determine functions of LDs observed in different cell types. although the presence of several proteins in LD is not yet understood, several data have shown that LDs act as a temporarily protein-storage depot, either to make some proteins inaccessible or to compartmentalize all the proteins involved in the same pathway. in immune cells or during the inflammatory response, several proteins are involved in lipid synthesis, lipolysis, eicosanoids synthesis, cell signaling, and immune response. it is noteworthy that the same protein may participate in more than one cellular process (image created with BioRender.com).

AA: Arachidonic acid, ADP: adenosine diphosphate, AGPAT3: 1-acylglycerol-3-phosphate O-acyltransferase 3, ATP: adenosine triphosphate, ATGL: Adipose triglyceride lipase, CAMP: cathelicidin, CCT: CTP:phosphocholine cytidylyltransferase, cPLA2: Cytosolic phospholipase A2, DAG: diglyceride, COX: cyclooxygenase, EXC4: eoxin C4, FA: fatty acids, FLAP: LO–activating protein, G0S2: G0/G1 Switch 2, GPAT4: Glycerol-3-phosphate acyltransferase 4, HSL: Hormone-sensitive lipase, IFI47: Interferon gamma inducible protein 47, IGTP: interferon-inducible guanosine triphosphatases, IRAK1: Interleukin 1 Receptor Associated Kinase 1, IRF3: Interferon regulatory factor 3, LO: lipoxygenase, LPLAT: Lysophospholipid acyltransferase, LT: Leukotriene, LTC4S: LTC4-synthase, MAG: Monoglycerides, MIF: migration inhibitory factor, PAP: phosphatidic acid phosphatase, PG: prostaglandin, PGES: prostaglandin E synthase, Plin: perilipin, PI3K: Phosphoinositide 3-kinases, PKC: Protein kinase C,TAG: triglycerides, TBK1: TANK-binding kinase 1, TGTP1: T-cell-specific guanine nucleotide triphosphate-binding protein 1, TNF: Tumor necrosis factor, TRAF6: TNF receptor associated factor 6.

Plin4 with CE-rich LDs, and finally, Plin2 and Plin3 were observed in both types of LDs [45].

LDs also have an active role in lipid metabolism, both in synthesizing neutral lipids and the release of fatty acid by lipolysis [32,46,47]. LD is an important site for neutral lipids synthesis during lipid loading, especially triglycerides (TAG) [31,32]. The synthesis of TAG on LD is mainly due to translocation ER-to-LD targeting of at least one isoform of the multienzyme complex that catalyzes the all sequential reactions involved in TAG synthesis from glycerol and fatty acids, including glycerol-3-phosphate O-acyltransferase 4 (GPAT4), 1-acylglycerol-3-phosphate O-acyltransferase 3 (AGPAT3), phosphatidic acid phosphatase/Lipin (PAP/Lipin), and DGAT2 [31,32,46,48] (Figure 1).

The LD-associated proteome has been reported the presence of two of the three main lipases involved in the hydrolysis of TAG, the adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL/LIPE), that cleaves the first and second fatty acid in the TAG, respectively [49,50]. In this case, the translocation of ATGL and HSL to LD is essential for lipolysis [49,51,52]. Moreover, the mechanism of regulation of TAG degradation is highly dependent on LD location of both Comparative Gene Identification-58 – (CGI-58)/ 1-acylglycerol-3-phosphate O-acyltransferase (ABHD5) [53–55], and ATGL coactivator protein, as well as the ATGL inhibitory protein (G0/G1 switch gene2 – G0S2) [56]. The regulation of lipolysis also involves the participation of structural proteins of LDs [57,58]. In this context, Plin1, Plin2, and Plin3 sterically shield LDs from lipolysis, and the degradation of these proteins acts as a prerequisite to stimulate both ATGL lipolysis and macrolipophagy [24,59,60]. Furthermore, Plin1 also restricts basal lipolysis by sequestering CGI-58 reversibly [55], while Plin5 has a central role in promoting and regulating lipolysis [49,50]. In this case, Plin5 promoting ATGL and HSL recruitment to LDs [49,52] and possibly forming high-molecular-weight assemblies Plin5- CGI-58 – ATGL is important in the regulation of lipolysis rates [50]. However, this mechanism does not happen on all cell types since the expression of Plin1 and Plin5 are limited to adipocytes and oxidative tissue [43,61,62]. Alternatively, hypoxia-inducible protein 2 (HIG2)/hypoxia-inducible lipid droplet-associated (HILPDA) have been reported as an inhibitor of ATGL-mediated lipolysis in macrophages [63,64]. Although the mechanism of inhibition of ATGL by HILPDA has not yet been fully elucidated, extensive homology shared between HILPA and G0S2 indicates that the mechanism of ATGL-inhibition of these proteins may be analogous [65,66].

In contrast to the synthesis of triglycerides in LDs, sterol esterification and phospholipid metabolism likely do not localize to LDs or happen in a more limited way in these organelles. Despite cholesterol ester being the predominant lipid in LDs in several cell types, especially in macrophages [34,67–70], ACAT enzymes seem to reside only at luminal ER [71,72]. Although ACAT could be located at RE in close proximity to LDs [35], the absence of esterification of cholesterol ester in LDs leaves several open questions about how the flow of cholesterol ester occurs from ER to growing LD. Still, in cholesterol metabolism, several Hydroxysteroid dehydrogenase family proteins (HSDs) have been localized on LDs, suggesting the ability of LDs to convert cholesterol to hormones [73]. The presence of phosphocholine cytidylyltransferase (CCT), cytosolic phospholipase A2 (cPLA2) [23,74], and lysophospholipid acyltransferases (LPLAT1 and LPCAT2) [75] suggested participation of these organelles in *de novo* biosynthesis and remodeling of phosphatidylcholine [75–77]. Moreover, cPLA2 activity also involves LD biogenesis [41,78–80] and eicosanoids synthesis onto LDs [74,80].

3. The functions of LDs in inflammation and immunity are dependent on their protein composition

The LD proteome has been reported as dynamic and complex, housing numerous proteins [20,36,81,82]. The great protein and lipid diversity inherently determine the functions of LDs observed in different cell types [15–17,24,83]. Moreover, LDs composition depends on the metabolic state of cells and stimulatory conditions [20,84,85]. Several data have shown that LDs act as a temporary protein-storage depot, and two distinct processes seem to be taking place, the protein sequestration and the spatial compartmentalization of cell pathways [5,20,86–88]

LDs' role as protein-sequestration sites has been associated with the down-regulation of the ability of hijacked proteins to interact with binding partners [7,8,15]. In addition, LD's protein-sequestration may also avoid ER stress and the cytotoxic potential of unfolded and damaged proteins [81,83,87,89]. Moreover, hijacked proteins in LD can be targeted to protein degradation by the proteasome or autophagy [90–92] and protein delivery to the target site [22,58,93]. These strategies were especially noted for histones in the LDs of *Drosophila* embryos. Despite being a cationic protein canonically involved in the formation and maintenance of nucleosomes [94], histones are cytotoxic when located in excess in the cytoplasm [94–96]. Compartmentalization of histones on LDs and involved the participation of the LD protein Jabba [97], they are released according to the demand generated by DNA replication [97] or in response to the presence of bacterial cell wall components [93].

It is now widely appreciated that that LDs also act as sites compartmentalizing entire signaling and metabolic pathways [23,58,98]. In this process, the LD acts as a scaffolding structure allowing all proteins of the same pathway to be assembled in the same site, facilitating the occurrence of several cellular processes [16,17,29]. Moreover, LD's compartmentalization of signaling and metabolic pathways are also involved in inflammatory and infectious diseases [26,30,99]. However, the mechanisms that lead to protein sequestration or compartmentalization of a pathway in LDs are not fully elucidated. In the immune response, the LD proteome has been associated mainly with lipid homeostasis, eicosanoids synthesis, innate immune response, and cell signaling (Figure 1), which will be explored further below.

3.1. LDs as a platform for the synthesis of inflammatory mediators

Substantial evidence has demonstrated that LDs are specialized intracellular sites for eicosanoid synthesis, often associated with

the inflammatory, infectious and neoplastic processes [40,100–105]. Eicosanoids are bioactive lipids derived from enzymatic oxygenation of arachidonic acid via the cyclooxygenase (COX) and lipoxygenase (LO) pathways [4,26]. Eicosanoids act in several cellular processes, including tissue homeostasis, host defense, and inflammation [16,26,106,107]. Several studies have demonstrated that the orchestration of each lipid mediator by its time, duration, and magnitude is essential for the biological function of eicosanoids [4,108].

LDs are one of the main storage sites of arachidonic acid (AA), esterified in phospholipids on the LD monolayer and triglycerides at the LD core. In leukocytes, electron microscopic autoradiographic studies with radiolabeled arachidonate demonstrated that exogenous AA was incorporated prominently in LDs of eosinophils, neutrophils, macrophages, mast cells, and epithelial cells [109–112]. Lipid analysis of purified LDs obtained by subcellular fractionation demonstrated that arachidonate was incorporated predominantly in the phospholipid pool of eosinophils; whereas arachidonic acid-containing neutral lipids appear to be the major store of arachidonic acid in monocyte/macrophages, neutrophils and mast cells [23,113,114]. Moreover, in LD proteome also have phospholipases (e.g. $cPLA_2$) and lipases (e.g. ATGL and HSL), key enzymes for the mobilization of arachidonic acid esterified within phospholipids or triglycerides, respectively [23,47,110,114,115]. In addition to these enzymes, LDs compartmentalize the entire enzymatic machinery for eicosanoid synthesis, including activating kinases involved in the arachidonic acid mobilization pathway (ERK1/2, p38, and p85) [23], and all relevant eicosanoid-forming enzymes (COX-1, COX-2, 5-LO, 5-LO–activating protein, 15-LO, LTC_4-synthase, and PGE-synthase) [40,105]. The compartmentalization of all this machinery causes LDs to be capable of rapid arachidonic acid mobilization to produce several eicosanoids, in especial prostaglandins and leukotrienes [4,23,25,108] (Figure 1). As a result of this process, stimuli that induce or inhibit LD formation also coordinately enhance or inhibit eicosanoid synthesis, respectively, in a dose-dependent manner [15,26]. Direct proof of eicosanoid synthesis occurring within LDs came after the development of a lipid immunolabeling technique termed EicosaCell [108]. Since eicosanoids are newly formed and non-storable, this method enable to immobilize and label eicosanoids at the exact locale of their synthesis and has given further insight into the functions of LDs in subcellular protein organization and signaling.

During inflammatory and/or infectious stimulation, it has been experimentally demonstrated that LDs could be the main sites of production of eoxin C_4 (EXC_4) [103], leukotriene B_4 (LTB_4) [40,116], leukotriene C_4 (LTC_4) [40,117], prostaglandin D_2 (PGD_2) [104], prostaglandin E_2 (PGE_2) [102,118,119] and 15(S)-hydroxyeicosatetraenoic acid (15(S)-HETE) [120] depending on the stimulus in different cell types. Other data further indicate that LDs probably are the main synthesis site of cysteinyl leukotriene (Cys-LT) [121], lipoxin B_4 (LXB_4) [12], and prostaglandin F2alpha (PGF2α) [12,122], due to the stronger correlation reported between LD accumulation and the generation of these eicosanoids. Interestingly, despite the strong correlation between LD accumulation and synthesis of several eicosanoids in the literature, the connection of LDs and the synthesis of mediators derived from eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), including resolvins, protectins, and maresines, are still poorly investigated.

3.2. LDs as an innate immune hub

Innate immune receptors, including TLR2 and TLR4, and nuclear receptors play major roles in infection-driven LD biogenesis [17]. TLRs activated by pathogens and/or pathogen-derived molecules trigger signaling pathways that are involved in the formation of LDs in host infected cells and also trigger the indirect mechanisms of activation of bystander amplification-induced system through host-generated cytokines and chemokines, thus suggesting that LDs as an integral part of innate immune response.

Indeed, LDs are now recognized as central players in interferon (IFN) responses, both in signaling pathways and the effectiveness of the response [92,123,124]. Moreover, LDs are required to enhance the synthesis of IFNs in infected cells, which is important for an effective early innate response to viral infection [124,125]. IFNs constitute a large signaling protein family, which regulate a myriad of proteins critical to the innate host response against microbial infections [126–128]. INF signaling also is a key modulator of lipid metabolism [70,129] and LD's protein composition [130–132].

Recent studies have established that LDs are functional hubs for innate immune proteins induced by interferon response [92,123–125]. During the immune response, multiple INF-inducible GTPases (IRGs) have found clustered with PLIN2 on LD proteome, including immunity-related GTPase M (IRGM1 and IRGM3)/Interferon-inducible guanosine triphosphatases (IGTP), Interferon-inducible GTPase 1 (IIGP1), T-cell-specific guanine nucleotide triphosphate-binding protein 1 (TGTP1), and Interferon-gamma inducible protein 47 (IFI47) [58,133]. The IRGs are involved in controlling several host defense processes essentials to the degradation of pathogen/parasite-containing vacuoles, including the phagocyte oxidase, antimicrobial peptides, and autophagy effectors [127,133–136]. Furthermore, the same data have been suggested that IRGs onto LDs are also involved in the cross-presentation of antigens in the dendritic cell [18,132,137]

The participation of LDs in innate cell-autonomous resistance also involves the compartmentalization of two potent antimicrobial proteins, the viperin [123,130,138] and the cathelicidin [133]. Viperin is a radical *S*-adenosylmethionine (SAM) enzyme regulated by IFN response to viral infection [131,139,140]. Viperin inhibits viral entry, replication, assembly, and budding through its physical interaction with several viral proteins, as well as its enzymatic action, catalyzing the production of the 3′-deoxy-3′,4′-didehydro-cytidine triphosphate (ddhCTP), an endogenous antiviral molecule [123,139,141–144]. In turn, cathelicidins are cationic peptides with

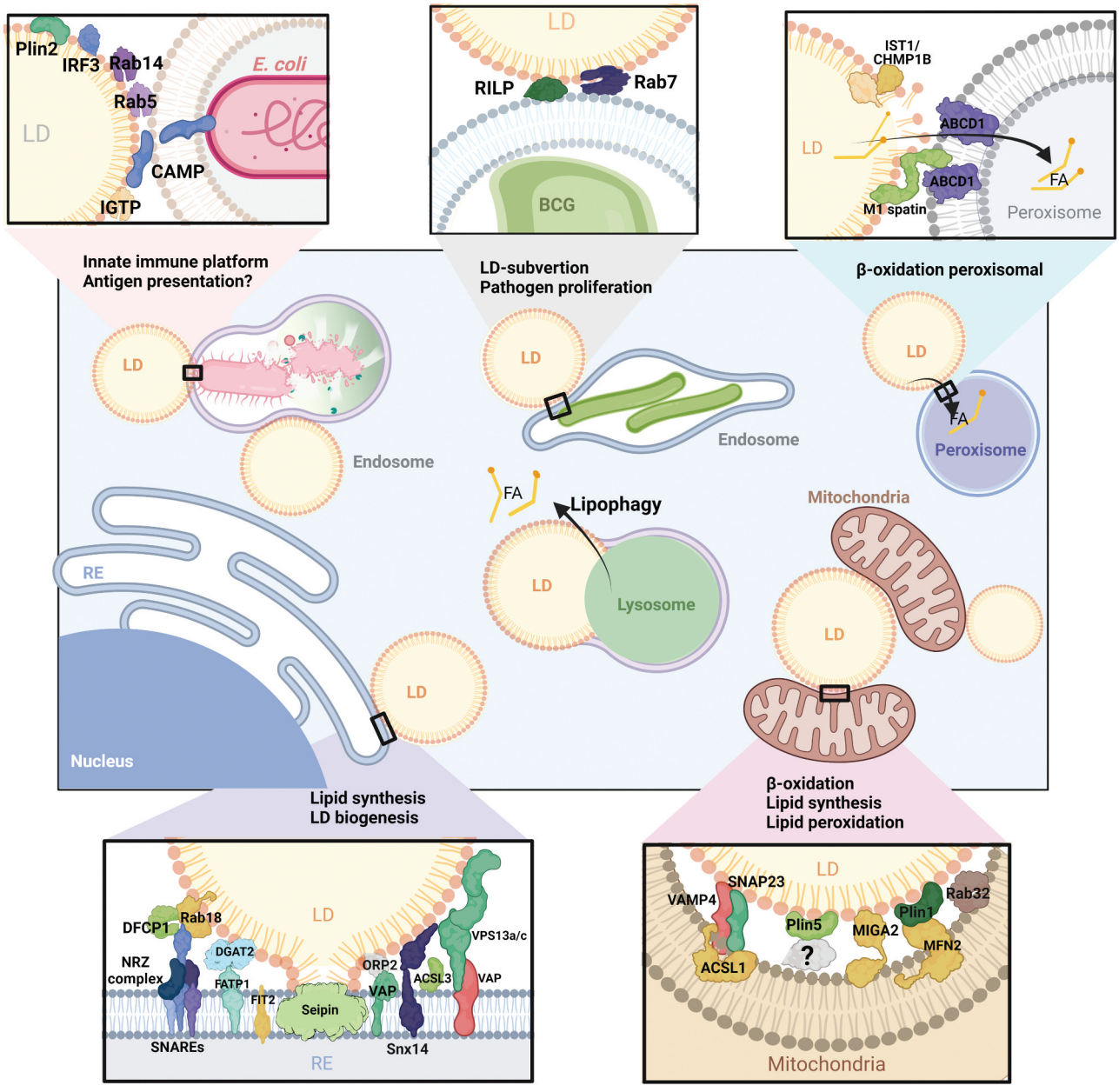

Figure 2. Lipid droplet–organelle contacts. Lipid droplets (LD) interact with nearly all organelles in the cell, including endoplasmic reticulum (ER), mitochondria, lysosome, peroxisome, and endosome. although the molecular basis for many of these contacts remains poorly understood, each LD interaction with other organelles is associated with specific proteins, implicated both in tethering structure as well as the organization of LDs contact sites are shown. although each organelle's contacts are represented here as distinct and spatially separate, recent data has been demonstrated that individual LDs can participate in contacts with multiple organelles simultaneously. tethering mechanisms that are thus far undefined are indicated by a question mark (image created with BioRender.com).

ABCD1: ATP-binding cassette, sub-family D (ALD), member 1, ACSL acyl-CoA synthetase, CAMP: Cathelicidin, DGAT2:diacylglycerol acyltransferase 2, FATP1: fatty acid transport protein 1, FIT2: Fat storage-inducing transmembrane protein 2, IGTP: Interferon gamma-induced GTPase, IRF3: Interferon regulatory factor 3, IST1/CHMP1B: Vacuolar protein sorting-associated protein IST1 /Charged multivesicular body protein 1b, MIGA2: Mitoguardin 2, MFN2: mitofusin 2, RILD: Rab-interacting lysosomal protein, NRZ: NAG–RINT1–ZW10 complex, PLIN: perilipin, SNARE: soluble NSF attachment receptor, SNAP23: Synaptosomal-associated protein 23, Snx14: Sorting Nexin 14, ORP2: oxysterol binding protein (OSBP)-related protein 2, VPS: Vacuolar protein sorting proteins, VAP: VAMP-associated proteins (VAPs), VAMP: Vesicle-associated membrane protein.

antimicrobial and immunomodulatory functions [145,146]. Due to their physicochemical characteristics as cationic peptides, cathelicidins can bind and inducing cell membrane damage, leading to microbial cell death [146–148]. Interestingly, the antibacterial mechanism of cathelicidins is similar to the one proposed for histones, the first antibacterial proteins to be reported to be loading to LDs in *Drosophilas* [93]. It is noteworthy that both viperin [149] and cathelicidin [150] have already been reported as essential modulators of lipid metabolism, which reinforces the interconnection of LDs' metabolic and immunological roles.

The autonomous immune response mechanism also connects with innate immune signaling. In this context, LD-localized viperin also might act as a scaffold for TLR7, TLR9, and Stimulator of Interferon Genes (STING) pathways, facilitating the production of type I IFN in immune cells [151,152]. In

this process, viperin recruits IRAK1 and TNF receptor-associated factor 6 (TRAF6) in a stimulation-dependent manner to LDs [151]. The co-localization of IRAK1 and TRAF6 by LD-localized viperin facilitates K63-linked ubiquitination of IRAK1 by TRAF6, which results in the interferon regulatory factor 7 (IRF7)-mediated induction of type I IFN production [151]. A similar role for LD-localized viperin in STING signaling was described in response to dsDNA, where viperin hijacking TANK-binding kinase 1 (TBK1) and STING, promoting the activation of TBK1 and, consequently, interferon production [152].

3.3. LDs as cellular signaling scaffold

Several well-established proteins with roles in key cell signaling have been reported within LDs [23,58,132]. In the LDs of leukocytes, some of the main protein kinases were found in LDs proteome, including Phosphoinositide 3-kinase (PI3K) subunits (p55, p88a, p88b), Mitogen-activated protein (MAP) kinases (ERK1, ERK2, and p38), Lyn tyrosine Kinase (Lyn), and Protein kinase C (PKC) [23,153–155]. In addition to the presence of these several kinases, functional studies demonstrate that LDs are important players in signal transduction and cell proliferation in inflammatory and neoplasic conditions [156,157].

Activation of LD associated proteins controls the rate of lipolysis of triglycerides, which is dependent on phosphorylation by PKA and PKC [158,159]. The phosphorylation of Plin1 (p-Plin1) leads to its dissociation from the GCI-58 factor, which promotes the activation of ATGL [49]. Moreover, p-Plin1 recruits HSL to LDs surface via the N-terminal region [51,98], favoring the phosphorylation and activation of HSL by PKC and ERK1/2 kinase pathways in adipocytes [51,52,160,161].

The presence of $cPLA_2$, PKC, PI3K, and MAP kinases on the surface of LDs are also key elements in regulating biological processes that occurs in LDs, particularly the lipolysis and the synthesis of eicosanoids [23,26,153]. The release of arachidonic acid and subsequent production of eicosanoids, cause PKC, PI3K, and MAPK/ERK to also have an important role in cPLA2 phosphorylation and activation [23,162–164]. In this context, the $cPLA_2$ and MAPK hijacking to the same site of the target proteins may facilitate the signaling involved in the activation of lipolysis and the release of AA esterified within phospholipids at the surface of LDs while ATGL have roles in releasing AA from triglicerydes [23,47,110,114,115].

4. LD interaction with other organelles enable bidirectional flux of contents

In addition to the protein hijacking to LDs, several cellular processes associated with LDs are due to these physical interactions with other cell compartments, including the ER, mitochondria, peroxisomes, Golgi apparatus, lysosomes, and endosomes [85,119,165–171]. The interorganelle contacts involve the membrane contact sites (MCS), specialized regions of the organellar membranes in close apposition between two organelles [172]. MSCs are established and maintained by protein tethering structures, which keep the two membranes close but without their fusion [172,173].

Mechanisms mediating and controlling LD association with other organelle are still not fully understood. Still, several data suggested that membrane trafficking proteins are a central player in this phenomenon, particularly SNARE protein [174,175] and the prenylated proteins of Rab GTPases family [76,165,175]. Furthermore, several articles highlighting the participation of Plin proteins in LD interaction with other organelles [58,176–178], both participating directly in the formation of tethering structures, as well as recruiting other proteins (Figure 2).

The MSCs favor the exchange of proteins and lipids between the LD and other organelles [27,172]. In particular, the interaction of LD with RE, mitochondria, and peroxisome may allow the coordination and regulation of the flux of lipid metabolites and the integration of lipid metabolism [179,180]. The lipid metabolism integration permits the lipids synthesized in the ER to be stored in the LDs, which later would be transferred lipids to various organelles, including mitochondria and peroxisomes [28,181]. On the other hand, the LDs' interaction with other organelles also has to be highlighted as a key process in the host-pathogen interaction [58,182,183], both in pro-host response and pathogens survival and replication.

4.1. LD-ER interaction

The LD-ER interaction is the most frequent interaction involving LDs [27,181]. Besides ER-derived organelles, LDs emerge as organelles that are partially or entirely distinct from the ER, and some data still indicate that LD could contain remnant ER-derived membranes [88,166]. Moreover, several data have shown overlap of the mechanisms involved in the LD-ER contact site with those related to the LD biogenesis cause all proteins involved in the LD-ER tethering structure are intimately involved in the LD biogenesis [8,88].

In the ER–LD contact site structure, Rab18 has been reported to be a key protein in maintaining these structures [175]. In this process, LD's Rab18 was found to physically associate with an ER-associated complex comprising the NRZ complex (with its subunits NAG, RINT1, and ZW10), associated with SNARE (Syntaxin 18, Use1, BNIP1) [175]. Still, in this context, Plin2 mediated the recruitment of Rab18 to LDs, formed a complex Plin2-Rab18-ACSL3 that contributed to TAG accumulation in myoblasts [184]. In addition to Rab18-NRZ-SNARE tether complex, ER-localized proteins Seipin [185,186], DFCP1 [187,188], fat-storage-inducing transmembrane protein 2 (FIT2) [189], human VPS13 protein (VPS13A and VPS13C) [190], OSBP-related proteins (ORP2) and its partner VAMP-associated proteins (VAP) [191], sorting nexin protein Snx14 [192], and Fatty acid transport protein 1 (FATP1)–DGAT2 complex [193] are also involved in LD-RE contact site. Interestingly, deletions or mutations in each of these proteins profoundly impact the number of contact sites and the amount of LD [194–201], suggesting that these proteins might act together, possibly through the formation of a macromolecular complex. However, this hypothesis still needs validation.

In addition to lipid metabolism integration, LD biogenesis and probably the maintenance LD-ER contact site could also contribute management of ER stress to unfolded protein,

a widespread consequence of inflammation and pathogenic infection [9,83,175,202]. On the other hand, LD-ER tethering protein could also be involved in the subversion of LD to support viral replication sites [28]. In this context, Rab18-mediated membrane trafficking of viral proteins to LDs facilitates viral replication and assembly [203–205]. The physical association between LDs and sites of viral replication is mediated by association Rab18 with the virus protein, such as HCV NS5A [203,204] or DENV NSP3 [205]. Furthermore, LD-associated protein PLIN3/TIP47 is an important mediator of anchorage of Hepatitis C Virus (HCV) nonstructural protein 5A (NS5A) and core protein [206,207], and the Dengue Virus (DENV) core protein [208] on LDs. The involvement of other proteins of LD-RE tethering structure in host-pathogens interaction still needs to be investigated, especially in leukocytes.

4.2. LD-mitochondria interaction

The LD-mitochondria contact is one of the most frequent and complex interactions involved with LDs in a wide variety of cell types, including the leukocytes [49,58,176,209]. Interestingly, LD structural proteins have been associated as the central player in LD-mitochondria interaction, particularly Plin1 and Plin5. In adipocytes under lipolytic conditions, the tethering structures between LD-mitochondria have been associated with Plin1 and the mitochondrial-associated protein MFN2 [178]. In contrast, the Plin5 was the principal protein responsible for the LD-mitochondria interaction in oxidative tissues [49,58,176]. Additionally, the participation of SNAP23, a SNARE protein [174], and Rab32 [210,211] in LD-mitochondria interaction was also associated with FA-induced LDs lipolysis to increase β-oxidation in adipocytes and hepatocytes, respectively.

In the meantime, the LD-mitochondria interaction is more complex than simply supplying lipids for β-oxidation. Recent data have been reported a more stable coupled between LD-mitochondria, also known as peridroplet mitochondria. Unlike isolated mitochondria, peridroplet mitochondria have reduced beta-oxidation capacity and promote LD expansion by providing ATP for triglyceride synthesis [168]. Curiously, these properties of peridroplet mitochondria were also associated with the expression of Plin5 [168]. The interaction LD-mitochondria favoring the synthesis of neutral lipids was also observed in the triple bound mitochondria-RE-LD when the MIGA2 binds directly to LDs and with VAP proteins in the ER [167]. One hypothesis that can explain these two sides of LD-mitochondria interaction is the existence of two types of contacts between these organelles, one more dynamic and another more stable [212]. However, the proteins involved in each process still need further investigation.

The interaction between LD-mitochondria is also a key element in regulating and modulating cellular metabolism in the inflammatory environment [58,209]. In this context, the dissociation of LD-mitochondria is essential for bacterial infections-triggered immunometabolic reprogramming in macrophages and liver [58,209]. In the liver, the dissociation of the LD-mitochondria interaction happens due to the decrease in the expression of Plin5, co-occurring with the increase of Plin2 and the clustering of several immune-related proteins on LDs [58]. Furthermore, maintenance of the association between LD- mitochondria in leukocytes was associated with amplifying cell damage in sepsis [209]. In this case, the oxidative microenvironment favors the oxidation of protein and lipid components of LDs in intimate contact with dysfunctional mitochondria, leading to an amplification of oxidative stress, both in macrophages and in the liver [209]. However, further details of this process still need to be better investigated. In leukocytes, the absence of Plin1 and Plin5 expression indicating that alternative mechanisms must be present in the LD-mitochondria interaction.

4.3. LD-endosomes interaction

During the parasite and bacterial infections, LDs are redistributed or recruited to the vicinity of pathogen-containing phagosome through mechanisms that involve complex pathogen- and host-derived signaling [119,213,214]. Physical interactions between LDs and phagosomes has been demonstrated, enabling bidirectional content exchange between LDs and phagosomes containing pathogens [100,118,215–217]. In *Mycobacterium bovis* infection, the late endosome protein Rab7 and its protein effector Rab-interacting lysosomal protein (RILP) were shown essential to the interaction between LD and *M. bovis* containing-phagosomes and also involves pathogen-derived cell wall molecules including lipoarabinomannan and PIM [165]. In turn, the capture and translocation of LD into the chlamydial inclusion have been associated with chlamydial protein Lda3 [218], probably forming a tethering structure between LDs and the inclusion membrane. Altogether, LD-phagosome interactions are controlled pathogen components, which enables the exchange of contents between LDs and phagosomes, and may represent a fundamental aspect of bacterial pathogenesis and immune evasion

The simultaneous presence of several Rab proteins, both LDs and EEs, probably strongly suggests that they may be involved in physical interaction between these organelles and/or the triple contact sites between EE-LD-RE [219,220]. Recent data have been reported 26 different Rab GTPases reside in the LD proteome, representing 20% of total proteins [85,90]. These findings corroborate the detection of Rab5 and Rab11 on purified LDs [220]. Moreover, several LD-resident Rab proteins are also present in early endosomes (EE), including Rab5, Rab8, Rab11, Rab13, Rab14, Rab15, and Rab21 [58,90,182]. Interestingly, the enrichment of Rab proteins in LDs happened concomitantly with the clusterization of antibacterial proteins in the LDs following lipopolysaccharide (LPS) stimulation [58]. Collectively, these data suggest Rab proteins may be involved in the LD-EE MSC, favoring the delivery of antibacterial proteins from LDs to phagosome-containing bacteria. Furthermore, among the Rab proteins enriched in the proteome of LDs, Rab14 and Rab34 deserve to be highlighted [58]. Both Rab14 and Rab34 are involved in antigen cross-presentation [221,222], which reinforces the participation of LDs in antigen presentation.

4.4. LD interaction with peroxisomes and lysosomes

Despite the interaction between LDs with peroxisomes and lysosomes often seen in various cell types, proteins associated with these processes remain to be elucidated [180,223]. In LD-

peroxisome interaction, M1 Spastin's seems to be the principal protein in the LD-peroxisomes complex. The M1 Spastin's have dual roles in LD-peroxisomes complex, directly participant da tether structure with peroxisomal -associated ABCD1, and recruiting membrane-shaping endosomal sorting complexes required for transport (ESCRT-III) components (IST1 and CHMP1B) to LD-peroxisome contact sites for FA trafficking [169]. However, the participation of peroxisomes in reprogramming the metabolism of macrophages is not yet fully understood.

LD-lysosome contact has been associated with autophagy-dependent processing of LDs, also known as macrolipophagy or lipophagy [223–225]. In this context, several indications suggest that autophagic cell machinery might be mediating LD-lysosome interaction [225–227]. However, it still needs to be validated. Another mechanism for LD-lysosomes interaction is through chaperone-mediated autophagy (CMA), lysosomal proteolysis carried by heat shock protein 70 (HSP70), and lysosome-associated membrane protein 2A (LAMP-2A) [228]. In this context, the degradation of Plin2 and Plin3 by CMA is a prerequisite to stimulate both ATGL lipolysis and macrolipophagy [57]. Beyond that, the induction of lipophagy is one mechanism in which the virus can subvert the lipid metabolism by increasing cellular β-oxidation, which generates ATP and can be used in viral replication and assembly [194,229,230].

5. Lipid droplet in the immunometabolism context

In the inflammatory context, LD formation is part of anabolic and glycolytic programming of pro-inflammatory leukocytes [12–14]. The activation of TLR, in especial TLR2, TLR3, TLR4, TLR5, TLR6, and TLR9, have been reported as key elements in the induction of LD accumulation in leukocytes [68,124,231–233]. Furthermore, TLR-driven LD biogenesis is a multimediated process that

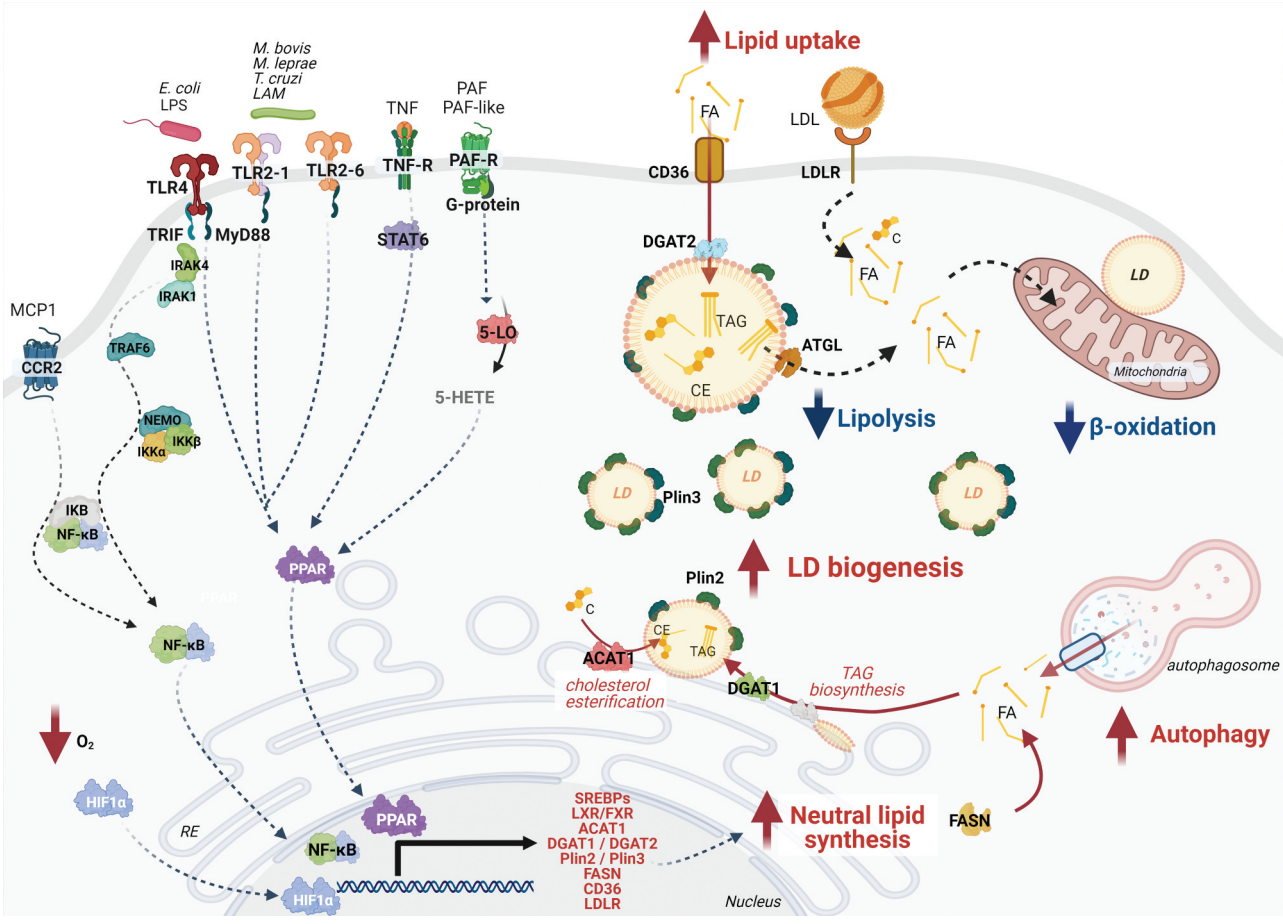

Figure 3. Lipid droplets biogenesis in inflammation and infection. lipid droplet (LDs) biogenesis is a highly regulated process involving several receptors of innate immunity, including TLR, which recognize pathogens or PAMPs (LAM, LPS). moreover, several cytokines (MCP-1/CCL2, TNF) and lipid mediator molecules (5-HETE, PAF, and PAF-like molecules) also induced the LDs accumulations. activation of the receptors of these molecules (TLR, TNF-R, PAF-R) started a complex signaling cascade (5-LO, STAT-6, Myd88, TRIF, IRAK, TRAF, MENO, IKK) that culminates in the activation of several transcription factors, such PPAR-γ, NFκB and or HIF1α. the activation of these transcription factors directly or indirectly increasing of the expression of several proteins involved in lipid synthesis (SREBPs, LXR/FXR, FASN, DGAT1, DGAT2, and ACAT1), lipid uptake (CD36, LDL-R), and autophagy as well as LD's structural proteins (Plin2 and Plin3). these transcription factors activation also decrease in expression and activity of lipolytic enzymes (ATGL), reduction of mitochondrial β-oxidation. this metabolic reprogramming favors the increase of synthesis or intracellular accumulation of fatty acid (FA) and cholesterol (C) and of their esterification in the form of cholesterol ester (CE) and triglycerides (TAG) by ACAT1 and DGAT1, respectively. all these events culminate in LD biogenesis and accumulation (image created with BioRender.com).

involves the increase of the expression of several receptors involved in lipid uptake and transport [214,233–235], decrease in expression of lipolytic enzymes [233,235], reduction of mitochondrial β-oxidation [183,195,196,236] and LD biogenesis [233,237]. The biogenesis of LD downstream of TLR activation is stronger dependent on *de novo* lipid synthesis, and in fact, the inhibition of the liponeogenesis severely impaired the LD accumulation [119,238] (Figure 3). Recent results have shown that each TLRs induces distinct lipidomes in macrophages, with significant changes in the main classes of lipids [197]. Since different TLRs recognize pathogens, different roles of this organelle in several infectious and inflammatory models can be due to modifications on quantities and variety of lipid composition of LDs.

The TLR-driven pathways also involve the activation of several transcription factors, such as Hypoxia Inducible Factor (HIF), Liver X receptor (LXR), Peroxisome Proliferator-Activated Receptors (PPARs), and Sterol Regulatory Element-binding protein (SREBPs) [12,38,198–201,214,216,239,240]. Members of the subfamily of these nuclear receptors are important sensors of the intracellular lipid environment and modulators of the expression of key genes in lipid synthesis, fatty acid uptake, cholesterol efflux, lipolytic enzymes, and LD biogenesis [38,39]. The regulation of lipid metabolism also involving the participation of other transcription factors in macrophages, including Pregnane X Receptors (PXRs), Vitamin D Receptor (VDR), REV-ERBα, the Nuclear Receptor 4A (NR4A), Farnesoid X Receptors (FXRs), and Estrogen-Related Receptors (ERRs) [241–248]. However, the participation of these transcription factors in LD accumulation in leukocytes during infection still needs further investigation.

Among transcription factors involved in LD accumulation, PPARs have been the most explored during the inflammation and infectious processes. PPARs are expressed by leukocytes, including lymphocytes, dendritic cells, and macrophages [38,249]. Several studies have demonstrated that the expression and function of the PPARs are regulated by bacterial components [198,250,251] and are often associated with LD biogenesis in leukocytes. Moreover, PPARs are highly expressed in foam cells within atherosclerotic lesions [252]. PPAR can directly impact LD formation, triggering *de novo* lipogenesis by modulating the expression of several genes, including fatty acid synthase (FASN) and Plin2, one of the principal LD structural proteins [253–255]. In BCG infection, PPARγ expression and LD formation largely depend on fatty acids translocase CD36 activation in association with CD11b/CD18 and CD14 compartmentalized on lipid rafts [214]. Moreover, there is a crosstalk of PPARs and other lipid metabolism regulatory factors, such as LXR and SREBPs [39]. PPAR functions counteregulate the role of NFκB, since have opposite roles in TLR2-triggered LD formation in BCG infection [214].

Furthermore, several molecules produced during the inflammatory response act in a paracrine manner, inducing LD formation, including lipid mediators, cytokines, and chemokines [116,118,119,215,231,256,257]. In this context, several pathways have been reported to accumulate from different stimuli, with intense cross-talk between these signals [116,237,258–260]. For example, Platelet-activating factor (PAF) or PAF-like induced LD formation through G protein-coupled PAF receptor, a mechanism dependent on 5-lipoxygenase (5-LO) activity to form 5(S)-hydroxyeicosatetraenoic acid (5-HETE) in polymorphonuclear leukocytes (PMN) [258,261]. In turn, PAF-induced LD biogenesis requires new protein synthesis that may be amplified by PPARγ activation and has intense crosstalk with chemokine ligand 2 (CCL2/MCP-1) signaling [237,258–260]. CCL2, also directly induces a dose-dependent increase in the numbers of cytoplasmic LDs in resident peritoneal macrophages through its cognate receptor CCR2, MAP kinases, ERK, and PI3K downstream signaling and requires the maintenance of a well-organized microtubule [116]. These redundant LD-triggering mechanisms indicated a central role of these organelles in the response of leukocytes.

In infectious disease, the participation of LDs has been reported for all classes of pathogens, from viruses [208,262] to protozoa [217,263], including bacteria [231,264] and fungi [265]. Host LDs may also be exploited to adapt higher specialized pathogens to escape the immune system and as an energy source for intracellular pathogens survival and/or replication [93,130,133]. However, recent results have been promoting a drastic transformation of the role of LDs in the infectious and inflammatory context. In this new perspective, several works have been shown a pro-host role of LDs [12,58,93,130,133]. In the pro-host context, LD improving the immune response act as an innate immune hub [58], as well as an important platform for the production of a broad range of host protective eicosanoids, such as leukotriene B_4 (LTB_4) and prostaglandins E_2 (PGE_2) [12,116]. In addition, the synthesis of neutral lipids and LD accumulation are important enhancers of the pro-inflammatory profile of macrophages [14,121].

As a site of production of different eicosanoids, the LDs are also intimately involved in paracrine, autocrine, and/or intracrine signal transduction of these molecules in immune cells [4,103]. Furthermore, an expressive correlation has been reported in several models between LD accumulation and synthesis and/or secretion of several cytokines, mainly those regulated by eicosanoids [121,257,266]. For example, in neutrophils was observed an LTC_4 paracrine signal-transduction pathway that mediates the secretion of eosinophil granules, including cytokine IL-4 [266]. When the LD accumulation is impaired, the LTC_4 is inhibited, and consequently, the IL-4 secretion is impaired [266]. And a similar phenomenon may be happening in other models. In pro-inflammatory macrophages, LDs inhibition has been followed by the decreasing of the expression of IL-6 and IL-1β, whose phenomenon can be reversed by the replacement of PGE_2 [14]. In SARS-COV-2 infected-monocytes, the LD biogenesis impaired by DGAT1 inhibitor was followed by reduction of cysLT and LTB_4 synthesis and decreasing of CXCL10, IL-6, IL-8, and TNF [121]. And similarly, the blockade of LD accumulation also decreasing the PGE_2 synthesis and IL-10 levels in *Mycobacteria sp* and *Trypanosoma cruzi* infected-macrophages [118,119,231]. LDs may also have a direct role in the secretion of some cytokines because TNF and macrophage migration inhibitory factors (MIF) were reported in LDs from leukocytes [237,267,268]. However, the biological implication of a direct association between these cytokines and LDs remains to be understood.

Interestingly, LD accumulation has also been reported in anti-inflammatory macrophages, also known as M2. Although M2 metabolic programming of macrophages has

been associated with lipolytic metabolism [269–271], some stimuli can trigger LD accumulation in anti-inflammatory profiles, too [231,239,272]. The presence of LD in an anti-inflammatory context was first observed in host-pathogen interaction, particularly in *M.bovis, Mycobacterium leprae*, and *Trypanosoma cruzi* infection [119,232,238,257]. In these models, LDs act as the site of PGE_2 synthesis, associated with a decrease in Th1-type cytokines and an increase in interleukin- 10 (IL-10), favoring the pathogen survival [238,239,264]. Moreover, apoptotic cells also can enhancer the LDs accumulation in M2-like phenotypes of macrophages [119]. More recently, the association of LDs and PGE_2 synthesis was also observed in macrophages stimulated murine adipose-derived conditioned medium (ASCcm) [272]. Interestingly, the application of these ASCcm polarized-macrophages has a protective action in experimental colitis and sepsis [273]. Although the mechanisms that lead to LDs in M2 macrophages are not yet fully elucidated, some indications suggest that the mTOR/PPARγ pathway regulates both LD biogenesis and macrophage plasticity [214,272,274]. However, open questions remain how LD are regulated and contribute to the different macrophage phenotypes.

6. Expert opinion

It is now widely appreciated that the range of the LD's role have expanded from its original description as a lipid storage compartment to a full-range cellular organelle that actively participates in immunity and inflammation. Studies of LD composition and structural features have revealed that LDs contain a diverse array of proteins in addition to lipids. Accumulating evidence has indicated that LDs have a much more complex and plastic structure and composition than initially anticipated. According to the cell and stimulatory condition, LDs may compartmentalize a distinct set of proteins, and the heterogeneity of LD composition may determine different cellular functions. Our contemporary view of LDs places this organelle as an important regulator of different metabolic, inflammatory, and infectious diseases and a key leukocyte activation marker. In leukocytes and other cells involved in immunity and infectious conditions, LDs have been shown to have central roles in compartmentalizing the synthesis of inflammatory mediators leading to the heightened production of eicosanoids, cytokines and participating in the amplification of the inflammatory response.

Moreover, LDs are also sites for antimicrobial protein localization. Notably, LD biogenesis is highly induced during infection and is often found in close proximity to the ER, phagosomes, and mitochondria. LDs exhibit roles in host defense, but some pathogens have evolved strategies to explore LDs as escape mechanisms by highjack LDs for exploitation as a nutrient source and subverting the host immune response.

Although great advances in the understanding of the mechanisms of LD biogenesis and its roles in lipid metabolism and inflammatory mediator production have been achieved, critical questions remain about the formation and the functions that lipid droplets play in infectious diseases. In conclusion, recent studies have identified LDs as multifunctional organelles with key functions in lipid storage and cell signaling in inflammation and immunity, and as such, they are emerging as attractive target candidates for therapeutic intervention. Future studies will be necessary to characterize the role of LDs as targets for therapeutic intervention in infectious diseases that progress with increased LD accumulation.

Acknowledgments

We would like to recognize present and past members of the Laboratory of Immunopharmacology for their valuable contributions. We apologize to investigators whose relevant work has not been cited because of space constraints.

Funding

This manuscript was funded Fundação de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ, Brasil); Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq, Brasil); Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES, Brasil – Finance Code 001).

ORCID

Filipe S. Pereira-Dutra http://orcid.org/0000-0003-1917-2876
Patrícia T. Bozza http://orcid.org/0000-0001-8349-9529

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Lundquist PK, Shivaiah -K-K, Espinoza-Corral R. Lipid droplets throughout the evolutionary tree. Prog Lipid Res. [Internet]. 2020;78:101029.
2. Walther TC, Farese RV. Lipid droplets and cellular lipid metabolism. Annu Rev Biochem. [Internet]. 2012;81(1):687–714.
3. Coleman RA. The "discovery" of lipid droplets: a brief history of organelles hidden in plain sight. Biochim Biophys Acta - Mol Cell Biol Lipids. [Internet]. 2020;1865:158762.
4. Weller PF. 0 Leukocyte lipid droplets - Structure and function as "Eicosasomes." Trans Am Clin Climatol Assoc. [Internet]. 2016;127:328–340. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28066068
5. Olzmann JA, Carvalho P. Dynamics and functions of lipid droplets. Nat Rev Mol Cell Biol. [Internet]. 2019;20. Available from: http://dx.doi.org/10.1038/s41580-018-0085-z
6. Farese RV, Walther TC. Lipid droplets finally get a little R-E-S-P-E-C-T. Cell. 2009;139(5):855–860.
7. Welte MA. Expanding roles for lipid droplets. Curr Biol. [Internet]. 2015;25(11):R470–R481.
8. Pol A, Gross SP, Parton RG. Biogenesis of the multifunctional lipid droplet: lipids, proteins, and sites. J Cell Biol. [Internet]. 2014;204(5):635–646.
9. Petan T, Jarc E, Lipid JM. Droplets in cancer: guardians of fat in a stressful world. Molecules. [Internet]. 2018;23(8):1941.
10. Thiam AR, Beller M. The why, when and how of lipid droplet diversity. J Cell Sci. 2017;130:315–324.
11. Mashek DG. Hepatic lipid droplets: a balancing act between energy storage and metabolic dysfunction in NAFLD. Mol Metab. [Internet]. 2020;101115. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2212877820301897
12. Knight M, Braverman J, Asfaha K, et al. Lipid droplet formation in Mycobacterium tuberculosis infected macrophages requires IFN- γ/

HIF-1 α signaling and supports host defense. PLoS Negl Trop Dis. 2018;14:1–26.
13. Everts B, Amiel E, Huang S-C-C, et al. TLR-driven early glycolytic reprogramming via the kinases TBK1-IKKε supports the anabolic demands of dendritic cell activation. Nat Immunol. 2014;15 (4):323–332.
14. Castoldi A, Monteiro LB, Van Teijlingen Bakker N, et al. Triacylglycerol synthesis enhances macrophage inflammatory function. Nat Commun. [Internet]. 2020;11(1):4107.
15. Roingeard P, Melo RCN. Lipid droplet hijacking by intracellular pathogens. Cell Microbiol. 2017;19(1):e12688
16. Bozza PT, Magalhães KG, Weller PF. Leukocyte lipid bodies - Biogenesis and functions in inflammation. Biochim Biophys Acta - Mol Cell Biol Lipids. [Internet]. 2009;1791:540–551.
17. Pereira-Dutra FS, Teixeira L, Souza Costa MF, et al. Fat, fight, and beyond: the multiple roles of lipid droplets in infections and inflammation. J Leukoc Biol. [Internet]. 2019;106(3):563–580.
18. Vallochi AL, Teixeira L, Oliveira K Da S, et al. lipid droplet, a key player in host-parasite Interactions. Front Immunol. [Internet]. 2018;9. Available from: https://www.frontiersin.org/article/10.3389/fimmu.2018.01022/full
19. Herker E, Ott M. Emerging role of lipid droplets in host/pathogen interactions * lipid droplets : more than just fat storage. J Biol Chem. 2012;287(4):2280–2287.
20. Cermelli S, Guo Y, Gross SP, et al. The lipid-droplet proteome reveals that droplets are a protein-storage depot. Curr Biol. 2006;16(18):1783–1795.
21. Gao Q, Goodman JM. The lipid droplet—a well-connected organelle. Front Cell Dev Biol. 2015;3. 10.3389/fcell.2015.00049
22. Boucher DM, Vijithakumar V, Ouimet M. Lipid Droplets as Regulators of Metabolism and Immunity. Immunometabolism. 2021;3(3):e210021
23. Yu W, Bozza PT, Tzizik DM, et al. Co-compartmentalization of MAP kinases and cytosolic phospholipase A2 at cytoplasmic arachidonate-rich lipid bodies. Am J Pathol. 1998;152:759–769.
24. Ducharme NA, Bickel PE. Minireview: lipid droplets in lipogenesis and lipolysis. Endocrinology. 2008;149(3):942–949.
25. Bozza PT, Yu W, Cassara J, et al. Pathways for eosinophil lipid body induction: differing signal transduction in cells from normal and hypereosinophilic subjects. J Leukoc Biol. [Internet]. 1998;64 (4):563–569.
26. Bozza PT, Bakker-Abreu I, Navarro-Xavier RA, et al. Lipid body function in eicosanoid synthesis: an update. Prostaglandins Leukot Essent Fat Acids. [Internet]. 2011;85(5):205–213.
27. Schuldiner M, Bohnert M. A different kind of love – lipid droplet contact sites. Biochim Biophys Acta - Mol Cell Biol Lipids. [Internet]. 2017;1862:1188–1196.
28. Herker E, Vieyres G, Beller M, et al. Lipid droplet contact sites in health and disease. Trends Cell Biol. [Internet]. 2021;31 (5):345–358.
29. Bosch M, Parton RG, Pol A. Lipid droplets, bioenergetic fluxes, and metabolic flexibility. Semin Cell Dev Biol. [Internet]. 2020;0–1. Available from: https://doi.org/10.1016/j.semcdb.2020.02.010
30. Bozza PT, Viola JPB. Lipid droplets in inflammation and cancer. Prostaglandins, Leukot Essent Fat Acids. [Internet]. 2010;82(4–6):243–250.
31. Chitraju C, Walther TC, Farese RV. The triglyceride synthesis enzymes DGAT1 and DGAT2 have distinct and overlapping functions in adipocytes. J Lipid Res. 2019;60(6):1112–1120.
32. McFie PJ, Banman SL, Stone SJ. Diacylglycerol acyltransferase-2 contains a c-terminal sequence that interacts with lipid droplets. Biochim Biophys Acta - Mol Cell Biol Lipids. 2018;1863 (9):1068–1081.
33. Dove DE, Su YR, Zhang W, et al. ACAT1 deficiency disrupts cholesterol efflux and alters cellular morphology in macrophages. Arterioscler Thromb Vasc Biol. [Internet]. 2005;25(1):128–134.
34. Zhu Y, Chen C-Y, Li J, et al. In vitro exploration of ACAT contributions to lipid droplet formation during adipogenesis. J Lipid Res. [Internet]. 2018;59(5):820–829.
35. Xu Y, Du X, Turner N, et al. Enhanced acyl-CoA: cholesterolacyltransferase activity increases cholesterol levels on the lipid droplet surface and impairs adipocyte function. J Biol Chem. [Internet]. 2019;294(50):19306–19321.
36. Wan H-CH-C, Melo RCN, Weller PF, et al. Roles and origins of leukocyte lipid bodies: proteomic and ultrastructural studies. FASEB J. [Internet]. 2006;21(1):167–178.
37. Bozza PT, Bandeira-melo C. Mechanisms of leukocyte lipid body formation and function in inflammation. Mem Inst Oswaldo Cruz. 2005;100(suppl 1):113–120.
38. Szatmari I, Töröcsik D, Agostini M, et al. PPARgamma regulates the function of human dendritic cells primarily by altering lipid metabolism. Blood. 2007;110(9):3271–3280.
39. Pawlak M, Lefebvre P, Staels B. Molecular mechanism of PPARα action and its impact on lipid metabolism, inflammation and fibrosis in non-alcoholic fatty liver disease. J Hepatol. [Internet]. 2015;62(3):720–733.
40. Silva AR, Pacheco P, Vieira-de-abreu A, et al. Lipid bodies in oxidized LDL-induced foam cells are leukotriene-synthesizing organelles: a MCP-1/CCL2 regulated phenomenon. Biochim Biophys Acta - Mol Cell Biol Lipids. 2009;1791(11):1066–1075.
41. Jarc E, Kump A, Malavašič P, et al. Lipid droplets induced by secreted phospholipase A2 and unsaturated fatty acids protect breast cancer cells from nutrient and lipotoxic stress. Biochim Biophys Acta - Mol Cell Biol Lipids. 2018;1863(3):247–265.
42. Brasaemle DL. Thematic review series: adipocyte Biology. the perilipin family of structural lipid droplet proteins: stabilization of lipid droplets and control of lipolysis. J Lipid Res. [Internet]. 2007;48 (12):2547–2559.
43. Itabe H, Yamaguchi T, Nimura S, et al. Perilipins: a diversity of intracellular lipid droplet proteins. Lipids Health Dis. [Internet]. 2017;16(1):83.
44. Greenberg AS, Egan JJ, Wek SA, et al. Perilipin, a major hormonally regulated adipocyte-specific phosphoprotein associated with the periphery of lipid storage droplets. J Biol Chem. 1991;266 (17):11341–11346.
45. Hsieh K, Lee YK, Londos C, et al.Perilipin family members preferentially sequester to either triacylglycerol-specific or cholesteryl-ester-specific intracellular lipid storage droplets. J Cell Sci. 2012, 125:4067–4076
46. Wilfling F, Wang H, Haas JT, et al. Triacylglycerol synthesis enzymes mediate lipid droplet growth by relocalizing from the ER to lipid droplets. Dev Cell. [Internet]. 2013;24(4):384–399.
47. Schlager S, Goeritzer M, Jandl K, et al. Adipose triglyceride lipase acts on neutrophil lipid droplets to regulate substrate availability for lipid mediator synthesis. J Leukoc Biol. 2015;98(5):837–850.
48. Wang H, Zhang J, Qiu W, et al. Lipin-1γ isoform is a novel lipid droplet-associated protein highly expressed in the brain. FEBS Lett. [Internet]. 2011;585(12):1979–1984.
49. Granneman JG, Moore H-PH, Mottillo EP, et al. Interactions of perilipin-5 (Plin5) with adipose triglyceride lipase. J Biol Chem. [Internet]. 2011;286(7):5126–5135.
50. Wang H, Bell M, Sreenevasan U, et al. Unique regulation of Adipose Triglyceride Lipase (ATGL) by Perilipin 5, a lipid droplet-associated protein. J Biol Chem. [Internet]. 2011;286(18):15707–15715.
51. Wang H, Hu L, Dalen K, et al. Activation of hormone-sensitive lipase requires two steps, protein phosphorylation and binding to the PAT-1 domain of lipid droplet coat proteins. J Biol Chem. [Internet]. 2009;284(46):32116–32125.
52. Whytock KL, Shepherd SO, Wagenmakers AJM, et al. Hormone-sensitive lipase preferentially redistributes to lipid droplets associated with perilipin-5 in human skeletal muscle during moderate-intensity exercise. Authors J Physiol C. 2018;596:2077–2090.
53. Yamaguchi T, Omatsu N, Matsushita S, et al. CGI-58 interacts with perilipin and is localized to lipid droplets. J Biol Chem. [Internet]. 2004;279(29):30490–30497.
54. Vieyres G, Reichert I, Carpentier A, et al. The ATGL lipase cooperates with ABHD5 to mobilize lipids for hepatitis C virus assembly [Internet]. PLoS Pathog. 2020;16(6):e1008554.

55. Subramanian V, Rothenberg A, Gomez C, et al. Perilipin A mediates the reversible binding of CGI-58 to lipid droplets in 3T3-L1 adipocytes. J Biol Chem. [Internet]. 2004;279(40):42062–42071.
56. Yang X, Lu X, Lombès M, et al. The G0/G1 switch gene 2 regulates adipose lipolysis through association with adipose triglyceride lipase. Cell Metab. [Internet]. 2010;11(3):194–205.
57. Kaushik S, Cuervo AM. Degradation of lipid droplet-associated proteins by chaperone-mediated autophagy facilitates lipolysis. Nat Cell Biol. [Internet]. 2015;17(6):759–770.
58. Bosch M, Sánchez-Álvarez M, Fajardo A, et al. Mammalian lipid droplets are innate immune hubs integrating cell metabolism and host defense. Science (80-). [Internet]. 2020;370(6514):eaay8085.
•• **The recent article demonstrated the role of LDs as an immunoplatform and modulator of immunometabolism.**
59. Brasaemle DL, Rubin B, Harten IA, et al. Perilipin A increases triacylglycerol storage by decreasing the rate of triacylglycerol hydrolysis. J Biol Chem. [Internet]. 2000;275(49):38486–38493.
60. Souza SC, De Vargas LM, Yamamoto MT, et al. Overexpression of perilipin A and B blocks the ability of tumor necrosis factor α to increase lipolysis in 3T3-L1 adipocytes. J Biol Chem. [Internet]. 1998;273(38):24665–24669.
61. Heid H, Rickelt S, Zimbelmann R, et al. On the formation of lipid droplets in human adipocytes: the organization of the perilipin–vimentin cortex. Iangowski J, editor. PLoS One. 2014;9(2):e90386.
62. Wang H, Sreenevasan U, Hu H, et al. Perilipin 5, a lipid droplet-associated protein, provides physical and metabolic linkage to mitochondria. J Lipid Res. 2011;52(12):2159–2168.
63. Van Dierendonck XAMH, De La Rosa Rodriguez MA, Georgiadi A, et al. HILPDA uncouples lipid droplet accumulation in adipose tissue macrophages from inflammation and metabolic dysregulation. Cell Rep. [Internet]. 2020;30(6):1811–1822.e6.
64. Maier A, Wu H, Cordasic N, et al. Hypoxia-inducible protein 2 Hig2/Hilpda mediates neutral lipid accumulation in macrophages and contributes to atherosclerosis in apolipoprotein E-deficient mice. FASEB J. 2017;31(11):4971–4984.
65. Zhang X, Saarinen AM, Hitosugi T, et al. Inhibition of intracellular lipolysis promotes human cancer cell adaptation to hypoxia. Elife. 2017;6:1–24.
66. Padmanabha Das KM, Wechselberger L, Liziczai M, et al. Hypoxia-inducible lipid droplet-associated protein inhibits adipose triglyceride lipase. J Lipid Res. 2018;59(3):531–541.
67. Jp A, Goo Y-h PAULA, Goo Y-H. Lipid droplet-associated proteins in atherosclerosis (Review). Mol Med Rep. [Internet]. 2016;13(6):4527–4534.
68. Nicolaou G, Goodall AH, Erridge C. Diverse bacteria promote macrophage foam cell formation via toll-like receptor-dependent lipid body biosynthesis. J Atheroscler Thromb. [Internet]. 2012;19(2):137–148.
69. Samanta D, Mulye M, Clemente TM, et al. Manipulation of host cholesterol by obligate intracellular bacteria. Front Cell Infect Microbiol. 2017;7:1–14.
70. York AG, Williams KJ, Argus JP, et al. Limiting cholesterol biosynthetic flux spontaneously engages type I IFN signaling. Cell. 2015;163(7):1716–1729.
71. Catherine CYC, Chen J, Thomas MA, et al. Regulation and immunolocalization of acyl-coenzyme A:cholesterol acyltransferase in mammalian cells as studied with specific antibodies. J Biol Chem. [Internet]. 1995;270(49):29532–29540.
72. Khelef N, Buton X, Beatini N, et al. Immunolocalization of acyl-coenzyme a: cholesterolo-acyltransferase in macrophages. J Biol Chem. [Internet]. 1998;273(18):11218–11224.
73. Liu Y, Xu S, Zhang C, et al. Hydroxysteroid dehydrogenase family proteins on lipid droplets through bacteria, C. elegans, and mammals. Biochim Biophys Acta - Mol Cell Biol Lipids. [Internet]. 2018;1863:881–894
74. Guijas C, Bermúdez MA, Meana C, et al. Neutral lipids are not a source of arachidonic acid for lipid mediator signaling in human foamy monocytes. 2019 [cited 2021 Mar 8]. Available from: www.mdpi.com/journal/cells
75. Moessinger C, Kuerschner L, Spandl J, et al. Human lysophosphatidylcholine acyltransferases 1 and 2 are located in lipid droplets where they catalyze the formation of phosphatidylcholine. J Biol Chem. [Internet]. 2011;286(24):21330–21339.
76. Guo Y, Walther TC, Rao M, et al. Functional genomic screen reveals genes involved in lipid-droplet formation and utilization. Nat. 2008;453(7195):657–661.
77. Krahmer N, Guo Y, Wilfling F, et al. Phosphatidylcholine synthesis for lipid droplet expansion is mediated by localized activation of CTP:phosphocholine cytidylyltransferase. Cell Metab. [Internet]. 2011;14(4):504–515.
78. Gubern A, Casas J, Barceló-Torns M, et al. Group IVA phospholipase A 2 is necessary for the biogenesis of lipid droplets. J Biol Chem. [Internet]. 2008;283(41):27369–27382.
79. Guijas C, Pérez-Chacón G, Astudillo AM, et al. Simultaneous activation of p38 and JNK by arachidonic acid stimulates the cytosolic phospholipase A 2 -dependent synthesis of lipid droplets in human monocytes. J Lipid Res. [Internet]. 2012;53(11):2343–2354.
80. Paloschi MV, Lopes JA, Boeno CN, et al. Cytosolic phospholipase A2-α participates in lipid body formation and PGE2 release in human neutrophils stimulated with an l-amino acid oxidase from Calloselasma rhodostoma venom. Sci Rep. [Internet]. 2020;10(1):10976.
81. Herms A, Bosch M, Ariotti N, et al. Cell-to-cell heterogeneity in lipid droplets suggests a mechanism to reduce lipotoxicity. Curr Biol. [Internet]. 2013;23(15):1489–1496.
82. Liu P, Ying Y, Zhao Y, et al. Chinese hamster ovary K2 cell lipid droplets appear to be metabolic organelles involved in membrane traffic. J Biol Chem. [Internet]. 2004;279(5):3787–3792.
83. Hapala I, Marza E, Ferreira T. Is fat so bad? Modulation of endoplasmic reticulum stress by lipid droplet formation. Biol Cell. 2011;103(6):271–285.
84. Larsson S, Resjö S, Gomez MF, et al. Characterization of the lipid droplet proteome of a clonal insulin-producing β-cell line (INS-1 832/13). J Proteome Res. [Internet]. 2012;11(2):1264–1273.
85. Zhang H, Wang Y, Li J, et al. Proteome of skeletal muscle lipid droplet reveals association with mitochondria and apolipoprotein A-I. J Proteome Res. 2011;10(10):4757–4768.
86. Yu J, Zhang S, Cui L, et al. Lipid droplet remodeling and interaction with mitochondria in mouse brown adipose tissue during cold treatment. Biochim Biophys Acta - Mol Cell Res. [Internet]. 2015;1853(5):918–928.
87. Marzluff WF, Tatomer DC. Histones: sequestered by Jabba in fatty storehouse. Curr Biol. [Internet] ;:. Available from. 2012;22(22):R951–R953.
88. Walther TC, Chung J, Farese RV. Lipid droplet biogenesis. Annu Rev Cell Dev Biol. [Internet]. 2017;33(1):491–510.
89. Bosma M, Dapito DH, Drosatos-Tampakaki Z, et al. Sequestration of fatty acids in triglycerides prevents endoplasmic reticulum stress in an in vitro model of cardiomyocyte lipotoxicity. Biochim Biophys Acta - Mol Cell Biol Lipids. 2014;1841(12):1648–1655.
90. Bersuker K, Peterson CWH, To M, et al. A proximity labeling strategy provides insights into the composition and dynamics of lipid droplet proteomes. Dev Cell. [Internet]. 2018;44(1):97–112.e7.
91. Drizyte-Miller K, Schott MB, Mcniven MA. Lipid droplet contacts with autophagosomes, lysosomes, and other degradative vesicles. Contact (Thousand Oaks), 20210, Jan 1; 3:1-13. doi:Doi: 10.1177/2515256420910892
92. Saka HA, Valdivia R. Emerging roles for lipid droplets in immunity and host-pathogen interactions. Annu Rev Cell Dev Biol. 2012;28(1):411–437.
93. Anand P, Cermelli S, Li Z, et al. A novel role for lipid droplets in the organismal antibacterial response. Elife. [Internet]. 2012;1:1–18. Available from: http://elifesciences.org/lookup/doi/10.7554/eLife.00003
• **First article to demonstrate a protective role of LDs in the antibacterial response**
94. Silk E, Zhao H, Weng H, et al. The role of extracellular histone in organ injury. Cell Death Dis. [Internet]. 2017;8(5):e2812.

95. Patat SA, Carnegie RB, Kingsbury C, et al. Antimicrobial activity of histones from hemocytes of the Pacific white shrimp. Eur J Biochem. 2004;271(23–24):4825–4833.
96. Chen R, Kang R, Fan X-G, et al. Release and activity of histone in diseases. Cell Death Dis. [Internet]. 2014;5(8):e1370.
97. Li Z, Thiel K, Thul PJ, et al. Lipid droplets control the maternal histone supply of Drosophila embryos. Curr Biol. 2012;22 (22):2104–2113.
98. Shen W-J, Patel S, Miyoshi H, et al. Functional interaction of hormone-sensitive lipase and perilipin in lipolysis. J Lipid Res. [Internet]. 2009;50(11):2306–2313.
99. Melo RCN, D'Avila H, Wan H-C, et al. Lipid bodies in inflammatory cells. J Histochem Cytochem. 2011;59(5):540–556.
100. Melo RCN, Ávila HD, Fabrino DL, et al. Macrophage lipid body induction by chagas disease in vivo: putative intracellular domains for eicosanoid formation during infection. Tissue Cell. 2003;35 (1):59–67.
101. Toledo DAM, Roque NR, Teixeira L, et al. Lipid body organelles within the parasite trypanosoma cruzi: a role for intracellular arachidonic acid metabolism elias MC, editor. PLoS One. 2016;11(8): e0160433.
102. Accioly MT, Pacheco P, Maya-Monteiro CM, et al. Lipid bodies are reservoirs of Cyclooxygenase-2 and sites of prostaglandin-E2 prostaglandin-E synthesis in colon cancer cells. Cancer Res. 2008;68(6):1732–1740.
103. Magalhães KG, Luna-Gomes T, Mesquita-Santos F, Corrêa R, et al. Schistosomal Lipids Activate Human Eosinophils via Toll-Like Receptor 2 and PGD2 Receptors: 15-LO Role in Cytokine Secretion.Front. Immunol. 2019, 9:3161. doi:DOI: 10.3389/fimmu.2018.03161
104. Luna-Gomes T, Magalhaes KG, Mesquita-Santos FP, et al. Eosinophils as a novel cell source of prostaglandin D2D2: autocrine role in allergic inflammation. J Immunol. [Internet]. 2011;187 (12):6518–6526.
105. Bozza PT, Yu W, Penrose JF, et al. Eosinophil lipid bodies: specific, inducible intracellular sites for enhanced eicosanoid formation. J Exp Med. 1997;186(6):909–920.
•• **Pioneering article in the demonstration of LDs as a compartmentalization platform for enzymes involved in the synthesis of eicosanoids.**
106. Bannenberg G, Arita M, Serhan CN. Endogenous Receptor Agonists: resolving Inflammation. Sci World J. [Internet]. 2007;7:1440–1462. Available from: http://www.hindawi.com/journals/tswj/2007/692896/abs/
107. Hamilton B, Ware LB, Matthay MA. Lipid mediators in the pathogenesis and resolution of sepsis and ARDS. 2018;3–11.
108. Bandeira-Melo C, Paiva LA, Amorim NRT, et al. Signal transduction immunohistochemistry [Internet], p.127-141. Kalyuzhny AE. editor. Methods mol biol. New York: Springer New York; 2017. Available from: http://link.springer.com/10.1007/978–1–4939–6759–9
109. Weller PF, Ackerman SJ, Nicholson-Weller A, et al. Cytoplasmic lipid bodies of human neutrophilic leukocytes. Am J Pathol. [Internet]. 1989;135:947–959. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2510521
110. Weller PF, Monahan-earley RA, Dvorak HF, et al. Cytoplasmic lipid bodies of human eosinophils subcellular isolation and analysis of arachidonate incorporation. Am J Pathol. 1991;138:141–148.
111. Plotkowski M-C, Brandão BA, De Assis M-C, et al. Lipid body mobilization in the ExoU-induced release of inflammatory mediators by airway epithelial cells. Microb Pathog. [Internet]. 2008;45(1):30–37.
112. Galli SJ, Dvorak AM, Peters SP, et al. Lipid bodies: widely distributed cytoplasmic structures that represent preferential nonmembrane repositories of exogenous [3H] arachidonic acid incorporeted by mast cells, macrophages and other cell types. In: Bailey JM, editors. Prostaglandins, Leukot Lipoxins. New York (NY): Plenum Publishing; 1985. p. 231–239.
113. Triggiani M, Oriente A, Seeds MC, et al. Migration of human inflammatory cells into the lung results in the remodeling o f arachidonic acid into a triglyceride pool. J Exp Med. 1995;182 (5):1181–1190.
114. Dichlberger A, Schlager S, Maaninka K, et al. Adipose triglyceride lipase regulates eicosanoid production in activated human mast cells. J Lipid Res. [Internet]. 2014;55(12):2471–2478.
115. Van Manen H-J, Kraan YM, Roos D, et al. Single-cell Raman and fluorescence microscopy reveal the association of lipid bodies with phagosomes in leukocytes. Proc Natl Acad Sci. [Internet]. 2005;102 (29):10159–10164.
116. Pacheco P, Vieira-de-abreu A, Gomes RN, et al. Monocyte chemoattractant protein-1/CC chemokine ligand 2 controls microtubule-driven biogenesis and leukotriene B4-synthesizing B4 - synthesizing function of macrophage lipid bodies elicited by innate immune response. J Immunol. [Internet] 2007;179(12):8500–8508.
117. Bandeira-Melo C, Phoofolo M, Weller PF. Extranuclear lipid bodies, elicited by CCR3-mediated signaling pathways, are the sites of chemokine-enhanced Leukotriene C 4 production in eosinophils and basophils. J Biol Chem. [Internet]. 2001;276(25):22779–22787.
•• **Pioneering article on the role of LDs in the synthesis of eicosanoids**
118. D'Avila H, Melo RCN, Parreira GG, et al. Mycobacterium bovis bacillus calmette-guérin induces tlr2-mediated formation of lipid bodies: intracellular domains for eicosanoid synthesis in vivo. J Immunol. 2006;176(5):3087–3097.
119. D'Avila H, Freire-de-lima CG, Roque NR, et al. Host cell lipid bodies triggered by trypanosoma cruzi infection and enhanced by the uptake of apoptotic cells are associated with prostaglandin E2 generation and increased parasite growth. J Infect Dis. [Internet]. 2011;204(6):951–961.
120. Weibel GL, Joshi MR, Wei C, et al. 15(S)-Lipoxygenase-1 associates with neutral lipid droplets in macrophage foam cells: evidence of lipid droplet metabolism. J Lipid Res. [Internet] 2009;50 (12):2371–2376.
121. Dias S Da SG, Soares VC, Ferreira AC, et al. Lipid droplets fuel SARS-CoV-2 replication and production of inflammatory mediators. Fouchier RAM, editor. PLOS Pathog. [Internet]. 2020;16(12): e1009127.
122. Araújo-santos T, Rodríguez NE, Moura-pontes S, et al. Role of prostaglandin F2α production in lipid bodies from leishmania infantum chagasi: insights on virulence. J Infect Dis. [Internet] 2014;210(12):1951–1961.
123. Seo J-Y, Yaneva R, Viperin: CP, et al. Interferon-inducible protein that regulates virus replication. Cell Host Microbe. [Internet]. 2011;10(6):534–539.
124. Monson E, Crosse K, Duan M, et al. Intracellular lipid droplet accumulation occurs early following viral infection and is required for an efficient interferon response. Nat Commun. 2021, 12, 4303. doi:DOI: 10.1038/s41467-021-24632-5
125. Monson EA, Crosse KM, Das M, et al. Lipid droplet density alters the early innate immune response to viral infection. PLoS One. 2018;13 (1):1–18.
126. Meunier E, Interferon-inducible BP. GTPases in cell autonomous and innate immunity. Cell Microbiol. 2016;18(2):168–180.
127. Petkova DS, Viret C, Faure M. IRGM in autophagy and viral infections. Front Immunol. 2012;3:1–7.
128. McNab F, Mayer-Barber K, Sher A, et al. Type I interferons in infectious disease. Nat Rev Immunol. 2015;15(2):87–103.
129. Blanc M, Hsieh WY, Robertson KA, et al. Host defense against viral infection involves interferon mediated down-regulation of sterol biosynthesis. PLoS Biol. 2011;9.
130. Hinson ER, Cresswell P. The antiviral protein, viperin, localizes to lipid droplets via its N-terminal amphipathic ?-helix. Proc Natl Acad Sci. [Internet]. 2009;106(48):20452–20457.
• **The first article demonstrates the presence of viperin in LDs**
131. Helbig KJ, Lau DTY, Semendric L, et al. Analysis of ISG expression in chronic hepatitis C identifies viperin as a potential antiviral effector. Hepatology. 2005;42(3):702–710.
132. Bougnères L, Helft J, Tiwari S, et al. A role for lipid bodies in the cross-presentation of phagocytosed antigens by MHC class i in dendritic cells. Immunity. 2009;31(2):232–244.
133. Haldar AK, Saka HA, Piro AS, et al. IRG and GBP host resistance factors target aberrant, "Non-self" Vacuoles characterized by the

missing of "Self" IRGM proteins. monack DM, editor. PLoS Pathog. [Internet]. 2013;9(6):e1003414.

- **The article first demonstrated the presence of protective proteins in LD in response to parasitic infection.**

134. Tiwari S, Choi HP, Matsuzawa T, et al. Targeting of the GTPase Irgm1 to the phagosomal membrane via PtdIns(3,4)P2 and PtdIns (3,4,5)P3 promotes immunity to mycobacteria. Nat Immunol. 2009;10(8):907–917.
135. Biering SB, Choi J, Halstrom RA, et al. Viral replication complexes are targeted by LC3-guided interferon-inducible GTPases. Cell Host Microbe. 2017;22(1):74–85.e7.
136. Murray HW, Mitchell-Flack M, Taylor GA, et al. IFN-γ-induced macrophage antileishmanial mechanisms in mice: a role for immunity- related GTPases, Irgm1 and Irgm3, in leishmania donovani infection in the liver. Exp Parasitol. 2015;157:103–109.
137. Brok Den MH, Raaijmakers TK, Collado-camps E, et al. Lipid droplets as immune modulators in myeloid cells. Trends Immunol. [Internet]. 2018;xx:1–13. Available from: http://www.cell.com/trends/immunology/fulltext/S1471-4906(18)30023-1
138. Peña Cárcamo JR, Morell ML, Vázquez CA, et al. The interplay between viperin antiviral activity, lipid droplets and Junín mammarenavirus multiplication. Virology. [Internet]. 2018;514:216–229.
139. Fitzgerald KA. The interferon inducible gene: viperin. J Interf Cytokine Res. [Internet]. 2011;31(1):131–135.
140. Rabbani MAG, Ribaudo M, Guo J-T, et al. Identification of interferon-stimulated gene proteins that inhibit human parainfluenza virus Type 3. sandri-goldin RM, editor. J Virol. [Internet]. 2016;90(24):11145–11156.
141. Helbig KJ, Beard MR. The role of viperin in the innate antiviral response. J Mol Biol. [Internet]. 2014;426(6):1210–1219.
142. Duschene KS, Broderick JB. Viperin: a radical response to viral infection. Biomol Concepts. 2012;3(3):255–266.
143. Gizzi AS, Grove TL, Arnold JJ, et al. A naturally occurring antiviral ribonucleotide encoded by the human genome. Nat. 2018;558 (7711):610–614
144. Fenwick MK, Su D, Dong M, et al. structural basis of the substrate selectivity of viperin. Biochemistry. 2020;59(5):652–662.
145. Sonawane A, Santos JC, Mishra BB, et al. Cathelicidin is involved in the intracellular killing of mycobacteria in macrophages. Cell Microbiol. [Internet]. 2011;13(10):1601–1617.
146. Van Harten RM, Van Woudenbergh E, Van Dijk A, et al. Cathelicidins: immunomodulatory Antimicrobials. Vaccines (Basel). 2018;6(3):63.
147. Lei J, Sun LC, Huang S, et al. The antimicrobial peptides and their potential clinical applications. Am J Transl Res. 2019;11:3919–3931.
148. Kumar P, Kizhakkedathu J, Straus S. Antimicrobial peptides: diversity, mechanism of action and strategies to improve the activity and biocompatibility in vivo. Biomolecules. [Internet]. 2018;8(1):4.
149. Seo J-Y CP, Cresswell P. Viperin regulates cellular lipid metabolism during human cytomegalovirus infection. PLoS Pathog. [Internet]. 2013;9(8):e1003497.
150. Hoang-Yen Tran D, Hoang-Ngoc Tran D, Mattai SA, et al. Cathelicidin suppresses lipid accumulation and hepatic steatosis by inhibition of the CD36 receptor. Int J Obes. [Internet]. 2016;40 (9):1424–1434.
151. Saitoh T, Satoh T, Yamamoto N, et al. Antiviral protein viperin promotes toll-like receptor 7- and toll-like receptor 9-mediated type i interferon production in plasmacytoid dendritic cells. Immunity. [Internet]. 2011;34(3):352–363.
152. Crosse KM, Monson EA, Dumbrepatil AB, et al. Viperin binds STING and enhances the type-I interferon response following dsDNA detection. Immunol Cell Biol. [Internet]. 2021;99(4):373–391.
153. Suzuki M, Iio Y, Saito N, et al. Protein kinase Cη is targeted to lipid droplets. Histochem Cell Biol. [Internet]. 2013;139 (4):505–511.
154. Yu W, Cassara J, Weller PF. Phosphatidylinositide 3-kinase localizes to cytoplasmic lipid bodies in human polymorphonuclear leukocytes and other myeloid-derived cells. Blood. 2000;95 (3):1078–1085.
155. Chen JS, Greenberg AS, Wang SM. Oleic acid-induced PKC isozyme translocation in RAW 264.7 macrophages. J Cell Biochem. 2002;86 (4):784–791.
156. Cruz ALS, Barreto E De A, Fazolini NPB, et al. Lipid droplets: platforms with multiple functions in cancer hallmarks. Cell Death Dis. [Internet]. 2020;11. Available from: 10.1038/s41419-020-2297-3.
157. Cruz ALS, Carrossini N, Teixeira LK, et al.Cell cycle progression regulates biogenesis and cellular localization of lipid droplets. Mol Cell Biol. 2019; 39(9):e00374–18
158. Fricke K, Heitland A, Maronde E. Cooperative activation of lipolysis by protein kinase a and protein kinase c pathways in 3T3-L1 adipocytes. Endocrinology. 2004;145(11):4940–4947.
159. Thrush AB, Gagnon A, Sorisky A. PKC activation is required for TSH-mediated lipolysis via perilipin activation. Horm Metab Res. 2012;44(11):825–831.
160. Bergan HE, Kittilson JD, Sheridan MA. PKC and ERK mediate GH-stimulated lipolysis. J Mol Endocrinol. [Internet]. 2013;51 (2):213–224.
161. Greenberg AS, Shen WJ, Muliro K, et al. Stimulation of lipolysis and hormone-sensitive lipase via the extracellular signal-regulated kinase pathway. J Biol Chem. [Internet]. 2001;276(48):45456–45461.
162. Ishihara K, Miyazaki A, Nabe T, et al. Group IVA phospholipase A2 A2 participates in the progression of hepatic fibrosis. FASEB J. 2012;26(10):4111–4121.
163. Xu J, Weng Y-I, Simoni A, et al.Role of PKC and MAPK in cytosolic PLA 2 phosphorylation and arachadonic acid release in primary murine astrocytes. J Neurochem. 2002; 83(2):259–270
164. Lin -W-W, Chen BC. Distinct PKC isoforms mediate the activation of cPLA 2 and adenylyl cyclase by phorbol ester in RAW264.7 macrophages. Br J Pharmacol. [Internet]. 1998;125(7):1601–1609.
165. Roque NR, Lage SL, Navarro R, et al. Rab7 controls lipid droplet-phagosome association during mycobacterial infection. Biochim Biophys Acta - Mol Cell Biol Lipids. [Internet]. 2020;1865:158703.
166. Melo RCN, Paganoti GF, Dvorak AM, et al. The internal architecture of leukocyte lipid body organelles captured by three-dimensional electron microscopy tomography maya-monteiro CM, editor. PLoS One. 2013;8(3):e59578.
167. Freyre CAC, Rauher PC, Ejsing CS, et al. MIGA2 links mitochondria, the ER, and lipid droplets and promotes de novo lipogenesis in adipocytes. Mol Cell. [Internet]. 2019;76(5):811–825.e14.
168. Benador IY, Veliova M, Mahdaviani K, et al. Mitochondria bound to lipid droplets have unique bioenergetics, composition, and dynamics that support lipid droplet expansion. Cell Metab. [Internet]. 2018;27(4):869–885.e6.
169. Kong J, Ji Y, Jeon YG, et al. Spatiotemporal contact between peroxisomes and lipid droplets regulates fasting-induced lipolysis via PEX5. Nat Commun. [Internet]. 2020;11(1):578.
170. Valm AM, Cohen S, Legant WR, et al. Applying systems-level spectral imaging and analysis to reveal the organelle interactome. Nature. 2017;546(7656):162–167.
171. Redgrave T. Association of golgi membranes with lipid droplets (Pre-Chylomicrons) from within intestinal epithelial cells durinc absorption of fat. Aust J Exp Biol Med Sci. [Internet]. 1971;49 (2):209–224.
172. Prinz WA. Bridging the gap: membrane contact sites in signaling, metabolism, and organelle dynamics. J Cell Biol. 2014;205:759–769.
173. Bravo-Sagua R, Torrealba N, Paredes F, et al. Organelle communication: signaling crossroads between homeostasis and disease. Int J Biochem Cell Biol. [Internet]. 2014;50:55–59.
174. Jägerström S, Polesie S, Wickström Y, et al. Lipid droplets interact with mitochondria using SNAP23. Cell Biol Int [Internet]. 2009;33 (9):934–940.
175. Xu D, Li Y, Wu L, et al. Rab18 promotes lipid droplet (LD) growth by tethering the ER to LDs through SNARE and NRZ interactions. J Cell Biol. 2018;217(3):975–995.
176. Gemmink A, Daemen S, Kuijpers HJH, et al. Super-resolution microscopy localizes perilipin 5 at lipid droplet-mitochondria interaction

sites and at lipid droplets juxtaposing to perilipin 2. Biochim Biophys Acta - Mol Cell Biol Lipids. [Internet]. 2018;1863:1423–1432.
177. Ware LB, Fessel JP, May AK, et al. Plasma biomarkers of oxidant stress and development of organ failure in severe sepsis. Shock. 2011;36(1):12–17.
178. Boutant M, Kulkarni SS, Joffraud M, et al. Mfn2 is critical for brown adipose tissue thermogenic function. EMBO J. [Internet]. 2017;36 (11):1543–1558.
179. Hugenroth M, Bohnert M, Plotkowski M-C, et al. Come a little bit closer! Lipid droplet-ER contact sites are getting crowded. Biochim Biophys Acta - Mol Cell Res. [Internet] 2020;1867(2):118603.
180. Simmen T, Tagaya M. Organelle communication at membrane contact sites (MCS): from curiosity to center stage in cell biology and biomedical research. Adv Exp Med Biol. 2017;997:1–12.
181. Bohnert M. Tethering fat: tethers in lipid droplet contact sites. Contact. 2020;3:251525642090814.
182. Rab proteins and the compartmentalization of the endosomal system. Cold Spring Harb Perspect Biol. 2014; 6(11):a022616. doi: doi: 10.1101/cshperspect.a022616
183. Feingold KR, Wang Y, Moser A, et al. LPS decreases fatty acid oxidation and nuclear hormone receptors in the kidney. J Lipid Res. 2008;49(10):2179–2187.
184. Deng Y, Zhou C, Mirza AH, et al. Rab18 binds PLIN2 and ACSL3 to mediate lipid droplet dynamics. Biochim Biophys Acta - Mol Cell Biol Lipids. [Internet]. 2021;1866:158923.
185. Szymanski KM, Binns D, Bartz R, et al. The lipodystrophy protein seipin is found at endoplasmic reticulum lipid droplet junctions and is important for droplet morphology. Proc Natl Acad Sci U S A. 2007;104(52):20890–20895.
186. Salo VT, Li S, Vihinen H, et al. Seipin facilitates triglyceride flow to lipid droplet and counteracts droplet ripening via endoplasmic reticulum contact. Dev Cell. 2019;50(4):478–493.e9.
187. Li D, Zhao YG, Li D, et al. The ER-localized protein DFCP1 modulates ER-lipid droplet contact formation. Cell Rep. 2019;27 (2):343–358.e5.
188. Gao G, Sheng Y, Yang H, et al. DFCP1 associates with lipid droplets. Cell Biol Int. [Internet]. 2019; 43(12):1492–1504.
189. Choudhary V, Golani G, Joshi AS, et al. Architecture of lipid droplets in endoplasmic reticulum is determined by phospholipid intrinsic curvature. Curr Biol. 2018;28(6):915–926.e9.
190. Yeshaw WM, Van Der Zwaag M, Pinto F, et al. Human VPS13A is associated with multiple organelles and influences mitochondrial morphology and lipid droplet motility. Elife. 2019;8:1–37.
191. Kentala H, Pfisterer SG, Olkkonen VM, et al. Sterol liganding of OSBP-related proteins (ORPs) regulates the subcellular distribution of ORP–VAPA complexes and their impacts on organelle structure. Steroids. [Internet]. 2015;99:248–258.
192. Datta S, Liu Y, Hariri H, et al. Cerebellar ataxia disease-associated Snx14 promotes lipid droplet growth at ER-droplet contacts. J Cell Biol. 2019;218(4):1335–1351.
193. Xu N, Zhang SO, Cole RA, et al. The FATP1-DGAT2 complex facilitates lipid droplet expansion at the ER-lipid droplet interface. J Cell Biol. 2012;198(5):895–911.
194. Ahmad L, Mostowy S, Sancho-Shimizu V. Autophagy-virus interplay: from cell biology to human disease. Front Cell Dev Biol. [Internet]. 2018;6:1–8. Available from: https://www.frontiersin.org/article/10.3389/fcell.2018.00155/full
195. Zager RA, Johnson ACM, Hanson SY. Renal tubular triglyercide accumulation following endotoxic, toxic, and ischemic injury. Kidney Int. 2005;67(1):111–121.
196. Keller H, Dreyer C, Medin J, et al. Fatty acids and retinoids control lipid metabolism through activation of peroxisome proliferator-activated receptor-retinoid X receptor heterodimers. Proc Natl Acad Sci U S A. 1993;90(6):2160–2164.
197. Hsieh W-Y, Zhou QD, York AG, et al. Toll-like receptors induce signal-specific reprogramming of the macrophage lipidome. Cell Metab. [Internet]. 2020;32(1):128–143.e5.
198. Szeles L, Torocsik D, Nagy L. PPARγ in immunity and inflammation: cell types and diseases. Biochim Biophys Acta - Mol Cell Biol Lipids. [Internet]. 2007;1771:1014–1030. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1388198107000364
199. Castrillo A, Joseph SB, Vaidya SA, et al.Crosstalk between LXR and toll-like receptor signaling mediates bacterial and viral antagonism of cholesterol metabolism. Molecular Cell. 2003;12:805–816
200. McRae S, Iqbal J, Sarkar-Dutta M, et al. The hepatitis C virus-induced NLRP3 inflammasome activates the sterol regulatory element-binding protein (SREBP) and regulates lipid metabolism. J Biol Chem. 2016;291(7):3254–3267.
201. Syed GH, Siddiqui A. Effects of hypolipidemic agent nordihydroguaiaretic acid on lipid droplets and hepatitis C virus. Hepatology. 2011;54(6):1936–1946.
202. Choi J-A, Song C-H. insights into the role of endoplasmic reticulum stress in infectious diseases. Front Immunol. [Internet]. 2020;10:3147. Available from: www.frontiersin.org
203. Salloum S, Wang H, Ferguson C, et al.Rab18 binds to hepatitis C Virus NS5A and promotes interaction between sites of viral replication and lipid droplets. PLoS Pathog. 2013;9(8):e1003513
204. Dansako H, Hiramoto H, Ikeda M, et al. Rab18 is required for viral assembly of hepatitis C virus through trafficking of the core protein to lipid droplets. Virology. [Internet]. 2014;462-463:166–174.
205. Tang W-C, Lin R-J, Liao C-L, et al. Rab18 facilitates dengue virus infection by targeting fatty acid synthase to sites of viral replication. J Virol. 2014;88(12):6793–6804.
206. Vogt DA, Camus G, Herker E, et al. Lipid droplet-binding protein TIP47 regulates hepatitis c virus rna replication through interaction with the viral NS5A protein. PLoS Pathog. 2013;9(4):1–14.
207. Ploen D, Hafirassou ML, Himmelsbach K, et al. TIP47 plays a crucial role in the life cycle of hepatitis C virus. J Hepatol. [Internet]. 2013;58(6):1081–1088.
208. Carvalho FA, Carneiro FA, Ic M, et al. Dengue virus capsid protein binding to hepatic lipid droplets (LD) is potassium ion dependent and is mediated by LD surface proteins. J Virol. [Internet]. 2012;86 (4):2096–2108.
209. Teixeira L, Souza-Moreira L, Prestes E, et al. Lipid droplets contribute to sepsis-associated organ dysfunction by disrupting tissue tolerance through the amplification of inflammation and lipid Peroxidation. SSRN Electron J. [Internet]. 2020;11:1400–1406. Available from: https://www.ssrn.com/abstract=3673486
210. Song Y-F, Hogstrand C, Ling S-C, et al. Creb-Pgc1α pathway modulates the interaction between lipid droplets and mitochondria and influences high fat diet-induced changes of lipid metabolism in the liver and isolated hepatocytes of yellow catfish. J Nutr Biochem. [Internet]. 2020;80:108364.
211. Li Q, Wang J, Wan Y, et al. Depletion of Rab32 decreases intracellular lipid accumulation and induces lipolysis through enhancing ATGL expression in hepatocytes. Biochem Biophys Res Commun. [Internet]. 2016;471(4):492–496.
212. Cui L, Liu P. Two types of contact between lipid droplets and mitochondria. Front Cell Dev Biol. [Internet]. 2020;8:1–11. Available from: https://www.frontiersin.org/articles/10.3389/fcell.2020.618322/full
213. Barisch C, Paschke P, Hagedorn M, et al. Lipid droplet dynamics at early stages of mycobacterium mycobacterium marinum infection in dictyostelium dictyostelium. Cell Microbiol. 2015;17(9):1332–1349.
214. Almeida PE, Roque NR, Magalhães KG, et al. Differential TLR2 downstream signaling regulates lipid metabolism and cytokine production triggered by Mycobacterium bovis BCG infection. Biochim Biophys Acta - Mol Cell Biol Lipids. 2014;1841 (1):97–107.
215. Peyron P, Vaubourgeix J, Poquet Y, et al. Foamy macrophages from tuberculous patients ' granulomas constitute a nutrient-rich reservoir for m tuberculosis persistence. PLoS Pathog. 2008;4(11):1–14.
216. Cao F, Castrillo A, Tontonoz P, et al. Chlamydia pneumoniae-induced pneumoniae -induced macrophage foam cell formation is mediated by toll-like receptor 2. Infect Immun. 2007;75(2):753–759.
217. Gomes AF, Magalhães KG, Rodrigues RM, et al. Toxoplasma gondii-skeletal muscle cells interaction increases lipid droplet

biogenesis and positively modulates the production of IL-12, IFN-g and PGE2. Parasit Vectors. [Internet]. 2014;7(1):47.
218. Cocchiaro JL, Kumar Y, Fischer ER, et al. Cytoplasmic lipid droplets are translocated into the lumen of the Chlamydia trachomatis parasitophorous vacuole. Proc Natl Acad Sci. [Internet]. 2008;105 (27):9379–9384.
219. Parton RG, Bosch M, Steiner B, et al. Novel contact sites between lipid droplets, early endosomes, and the endoplasmic reticulum. J Lipid Res. 2020;61(11):1364.
220. Liu P, Bartz R, Zehmer JK, et al. Rab-regulated interaction of early endosomes with lipid droplets. Biochim Biophys Acta Mol Cell Res. 2007;1773(6):784–793.
221. Weimershaus M, Maschalidi S, Sepulveda F, et al. Conventional dendritic cells require IRAP-Rab14 endosomes for efficient cross-presentation. J Immunol. 2012;188(4):1840–1846.
222. Alloatti A, Kotsias F, Pauwels A-M, et al. Toll-like receptor 4 engagement on dendritic cells restrains phago-lysosome fusion and promotes cross-presentation of antigens. Immunity. 2015;43 (6):1087–1100.
223. Pleet ML, Branscome H, Demarino C, et al. Autophagy, EVs, and infections : a perfect question for a perfect time. Front Cell Infect Microbiol. 2018;8:1–17.
224. Dugail I. Lysosome/lipid droplet interplay in metabolic diseases. Biochimie. 2014;96:102-5.
225. Schulze Rj, Krueger EW, Weller SG, et al. Direct lysosome-based autophagy of lipid droplets in hepatocytes. Proc Natl Acad Sci U S A. 2020; 117(51):32443–32452
226. Host C, Zhang JS, Lan Y, et al.Flaviviruses exploit the lipid droplet protein AUP1 to trigger lipophagy and drive virus production. Cell Host Microbe. 2018; 23(6):819–831.e5. doi:DOI: 10.1016/j.chom.2018.05.005
227. Onal G, Kutlu O, Gozuacik D, et al. Lipid droplets in health and disease. Lipids Health Dis. 2017;16(1):1–15.
228. Proikas-Cezanne T, Simos G, Liu X, et al.Emerging roles of lipophagy in health and disease. Front Cell Dev Biol . 2019; 7:185. doi: DOI: 10.3389/fcell.2019.00185
229. Heaton NS, Randall G. Dengue virus-induced autophagy regulates lipid metabolism. Cell Host Microbe. [Internet]. 2010;8(5):422–432.
230. Chan ST, Ou JJ. Hepatitis C virus-induced autophagy and host innate immune response. Viruses. 2017;5:1–10.
231. Mattos KA, Oliveira VGC, D'Avila H, et al. TLR6-driven lipid droplets in mycobacterium leprae-infected leprae-infected schwann cells: immunoinflammatory platforms associated with Bacterial Persistence. J Immunol. [Internet]. 2011;187(5):2548–2558.
232. D'Avila H, Melo RCN, Parreira GG, et al. Mycobacterium bovis bacillus calmette-guérin induces TLR2-mediated formation of lipid bodies: intracellular domains for eicosanoid synthesis in vivo. J Immunol. [Internet]. 2006;176(5):3087–3097.
233. Huang YL, Morales-Rosado J, Ray J, et al. Toll-like receptor agonists promote prolonged triglyceride storage in macrophages. J Biol Chem. 2014;289(5):3001–3012.
234. Mattos KA, Oliveira VCG, Berrêdo-Pinho M, et al. Mycobacterium leprae intracellular survival relies on cholesterol accumulation in infected macrophages: a potential target for new drugs for leprosy treatment. Cell Microbiol. [Internet]. 2014;16(6):797–815.
235. Hu X, Binns D, Reese ML. The coccidian parasites Toxoplasma and Neospora dysregulate mammalian lipid droplet biogenesis. J Biol Chem. 2017;292(26):11009–11020.
236. Drosatos K, Drosatos-Tampakaki Z, Khan R, et al. Inhibition of c-Jun-N-terminal kinase increases cardiac peroxisome proliferator-activated receptor α expression and fatty acid oxidation and prevents lipopolysaccharide-induced heart dysfunction. J Biol Chem. 2011;286(42):36331–36339.
237. Pacheco P, Bozza FA, Gomes RN, et al. Lipopolysaccharide-induced leukocyte lipid body formation in vivo: innate immunity elicited intracellular loci involved in eicosanoid metabolism. J Immunol. [Internet]. 2002;169(11):6498–6506.
•• **Pioneer article on the participation of TLRs in the induction of LD biogenesi.**
238. Mattos KA, Lara FA, Oliveira VGC, et al. Modulation of lipid droplets by Mycobacterium leprae in Schwann cells: a putative mechanism for host lipid acquisition and bacterial survival in phagosomes. Cell Microbiol. 2011;13(2):259–273.
239. Almeida PE, Silva AR, Maya-Monteiro CM, et al. Mycobacterium bovis bacillus calmette-guérin infection induces TLR2-dependent peroxisome proliferator-activated receptor γ expression and activation: functions in inflammation, lipid metabolism, and pathogenesis. J Immunol. [Internet]. 2009;183(2):1337–1345.
240. Mei C, He P, Cheng B, et al. Chlamydia pneumoniae induces macrophage-derived foam cell formation via PPAR α and PPAR γ-dependent pathways. Cell Biol Int. [Internet]. 2009;33(3):301–308.
241. Leopold Wager CM, Arnett E, Schlesinger LS. Macrophage nuclear receptors: emerging key players in infectious diseases. PLOS Pathog. [Internet]. 2019;15(3):e1007585.
242. Oh J, Riek AE, Darwech I, et al. Deletion of macrophage vitamin d receptor promotes insulin resistance and monocyte cholesterol transport to accelerate atherosclerosis in mice. Cell Rep. [Internet]. 2015;10(11):1872–1886.
243. Sui Y, Park SH, Helsley RN, et al. Bisphenol A increases atherosclerosis in pregnane X receptor-humanized ApoE deficient mice. J Am Heart Assoc. 2014;3(2):1–11.
244. Sitaula S, Billon C, Kamenecka TM, et al. Suppression of atherosclerosis by synthetic REV-ERB agonist. Biochem Biophys Res Commun. [Internet]. 2015;460(3):566–571.
245. Pei L, Castrillo A, Chen M, et al. Induction of NR4A orphan nuclear receptor expression in macrophages in response to inflammatory stimuli*. 2005 [cited 2021 Apr 29]. Available from: http://www.jbc.org
246. Giguère V. Transcriptional control of energy homeostasis by the estrogen-related receptors. Endocr Rev. 2008;29(6):677–696.
247. Francis M, Guo G, Kong B, et al. Regulation of lung macrophage activation and oxidative stress following ozone exposure by farnesoid x receptor. Toxicol Sci. 2020; 177(2):441–453
248. Barish GD, Downes M, Alaynick WA, et al.A nuclear receptor atlas: macrophage activation. Mol Endocrinol. 2005; 19(10):2466–77
249. Szanto A, Nagy L. Retinoids potentiate peroxisome proliferator-activated receptor gamma action in differentiation, gene expression, and lipid metabolic processes in developing myeloid cells. Mol Pharmacol. 2005;67(6):1935–1943.
250. Rajaram MVS, Brooks MN, Morris JD, et al. Mycobacterium tuberculosis activates human macrophage peroxisome proliferator-activated receptor gamma γ linking mannose receptor recognition to regulation of immune responses. J Immunol. 2010;185(2):929–942.
251. Mahajan S, Dkhar HK, Chandra V, et al. Mycobacterium tuberculosis modulates macrophage lipid-sensing nuclear receptors PPARγ and TR4 for Survival. J Immunol. 2012;188(11):5593–5603.
252. Tontonoz P, Nagy L, Alvarez JG, et al. PPARγ promotes monocyte/macrophage differentiation and uptake of oxidized LDL. Cell. 1998;93(2):241–252.
253. Larigauderie G, Furman C, Jaye M, et al. Adipophilin enhances lipid accumulation and prevents lipid efflux from THP-1 macrophages: potential role in atherogenesis. Arterioscler Thromb Vasc Biol. 2004;24(3):504–510.
254. Gao J, Serrero G. Adipose differentiation related protein (ADRP) expressed in transfected COS-7 cells selectively stimulates long chain fatty acid uptake. J Biol Chem. 1999;274(24):16825–16830.
255. Imamura M, Inoguchi T, Ikuyama S, et al. ADRP stimulates lipid accumulation and lipid droplet formation in murine fibroblasts. Am J Physiol Endocrinol Metab. 2002;283(4):E775–83.
256. Pacheco P, Bozza FA, Gomes RN, et al. Lipopolysaccharide-induced leukocyte lipid body formation in vivo: innate immunity elicited intracellular loci involved in. J Immunol. [Internet]. 2002;169 (11):6498–6506.
257. Mattos KA, D'Avila H, Rodrigues LS, et al. Lipid droplet formation in leprosy: toll-like receptor-regulated organelles involved in eicosanoid formation and Mycobacterium leprae pathogenesis. J Leukoc Biol. 2010;87(3):371–384.
258. Bozza PT, Payne JL, Goulet JL, et al. Mechanisms of platelet-activating factor-induced lipid body formation: requisite roles for 5-lipoxygenase and de novo protein synthesis in the

compartmentalization of neutrophil lipids. J Exp Med. 1996;183 (4):1515–1525.
259. Silva AR, De Assis EF, Caiado LFC, et al. Monocyte chemoattractant protein-1 and 5-lipoxygenase products recruit leukocytes in response to platelet-activating factor-like lipids in oxidized low-density lipoprotein. J Immunol. 2002;168(8):4112–4120.
260. De Assis EF, Silva AR, Caiado LF, et al. Synergism between platelet-activating factor-like phospholipids and peroxisome proliferator-activated receptor gamma agonists generated during low density lipoprotein oxidation that induces lipid body formation in leukocytes. J Immunol (Baltimore, Md 1950). 2003;171(4):2090–2098.
261. Prescott SM, Zimmerman GA, Stafforini DM, et al. Platelet-activating factor and related lipid mediators. Annu Rev Biochem. 2000;69(1):419–445.
262. Samsa MM, Mondotte JA, Iglesias NG, et al. Dengue virus capsid protein usurps lipid droplets for viral particle formation. PLoS Pathog. 2009;5(10):e1000632
263. Mota LAM, Roberto-Neto J, Monteiro VG, et al. Culture of mouse peritoneal macrophages with mouse serum induces lipid bodies that associate with the parasitophorous vacuole and decrease their microbicidal capacity against Toxoplasma gondii. Mem Inst Oswaldo Cruz. 2014;109(6):767–774.
264. D'Avila H, Roque NR, Cardoso RM, et al. Neutrophils recruited to the site of Mycobacterium bovis BCG infection undergo apoptosis and modulate lipid body biogenesis and prostaglandin E2 E2 production by macrophages. Cell Microbiol. 2008;10(12):2589–2604.
265. Sorgi CA, Secatto A, Fontanari C, et al. Histoplasma capsulatum cell wall -Glucan β-Glucan induces lipid body formation through CD18, TLR2, and dectin-1 receptors: correlation with leukotriene B4 B4 generation and role in HIV-1 Infection. J Immunol. 2009;182(7):4025–4035.
266. Neves JS, Radke AL, Weller PF. Cysteinyl leukotrienes acting via granule membrane-expressed receptors elicit secretion from within cell-free human eosinophil granules. J Allergy Clin Immunol. [Internet]. 2010;125(2):477–482.
267. Beil WJ, Weller PF, Peppercorn MA, et al. Ultrastructural immunogold localization of subcellular sites of TNF-α in colonic Crohn's disease. J Leukoc Biol. 1995;58(3):284–298.
268. Assunção-Miranda I, Amaral FA, Bozza FA, et al. Contribution of macrophage migration inhibitory factor to the pathogenesis of dengue virus infection. FASEB J. Internet]. 2010;24(1):218–228.
269. Pearce EL, Pearce EJ. Metabolic pathways in immune cell activation and quiescence. Immunity. 2013;38:633–643.
270. Laj O, Kishton RJ, Rathmell J. A guide to immunometabolism for immunologists. Nat Rev Immunol. 2016;16(9):553–565.
271. Tsao C-H, Shiau M-Y, Chuang P-H, et al. Interleukin-4 regulates lipid metabolism by inhibiting adipogenesis and promoting lipolysis. J Lipid Res. Internet]. 2014 [cited 2021 May 14];55 (3):385–397.
272. Souza-Moreira L, Soares VC, Da S, et al. Adipose-derived mesenchymal stromal cells modulate lipid metabolism and lipid droplet biogenesis via AKt/mtoR-ppARγ signalling in macrophages. Scientific Reports. 2019;9(1). 10.1038/s41598-019-56835-8.
273. Anderson P, Souza-Moreira L, Morell M, et al. Adipose-derived mesenchymal stromal cells induce immunomodulatory macrophages which protect from experimental colitis and sepsis. Gut. 2013;62(8):1131–1141.
274. Assunção LS, Magalhães KG, Carneiro AB, et al. Schistosomal-derived lysophosphatidylcholine triggers M2 polarization of macrophages through PPARγ dependent mechanisms. Biochim Biophys Acta - Mol Cell Biol Lipids. [Internet]. 2017;1862:246–254.