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REVIEW

Fat, fight, and beyond: The multiple roles of lipid droplets in infections and inflammation

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Abstract

Increased accumulation of cytoplasmic lipid droplets (LDs) in host nonadipose cells is commonly observed in response to numerous infectious diseases, including bacterial, parasite, and fungal infections. LDs are lipid-enriched, dynamic 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, LDs have come to be seen as an essential platform for various cellular processes, including metabolic regulation, cell signaling, and the immune response. LD participation in the immune response occurs as sites for compartmentalization of several immunometabolic signaling pathways, production of inflammatory lipid mediators, and regulation of antigen presentation. Infection-driven LD biogenesis is a complexly regulated process that involves innate immune receptors, transcriptional and post-transcriptional regulation, increased lipid uptake, and new lipid synthesis. Accumulating evidence demonstrates that intracellular pathogens are able to exploit LDs as an energy source, a replication site, and/or a mechanism of immune response evasion. Nevertheless, LDs can also act in favor of the host as part of the immune and inflammatory response to pathogens. Here, we review recent findings that explored the new roles of LDs in the context of host-pathogen interactions.

KEYWORDS
metabolism, lipid droplets, infection, inflammation

1 | INTRODUCTION

Lipids are a major and most diverse class of biomolecules, which play an important role in both the physiology and pathophysiology of living systems. In addition to acting as structural components of cell membranes, lipids are also energy sources as well as signaling molecules during infection and inflammation.[1–4] In the cell, the main lipid storage sites are lipid droplets (LDs) or lipid bodies, a ubiquitous organelle that can be found in virtually all types of cells from prokaryotes to multicellular eukaryotes.[5,6]

In recent decades, LDs have gone from being perceived as only a source of energy storage to being described as complex and dynamic organelles centrally involved in energy and lipid homeostasis, membrane biosynthesis, cell signaling, and handling of hydrophobic vitamin and cell protection to lipotoxicity.[7–13] Structurally, LDs are endoplasmic reticulum (ER)-derived organelles composed of a core of neutral lipids (triacylglycerol, diacylglycerol, and cholesterol ester) surrounded by a monolayer of phospholipids associated with a diverse composition of proteins.[14,15]

The size, number, function, and composition of LDs differ considerably among different cell types and even in individual cells in a population.[5,13,16] The LD proteome has been reported as dynamic and complex in several cell types and stimulatory conditions.[17–19] Accumulating data demonstrate not only the protein diversity but also the compartmentalization of signaling and metabolic pathways on LDs, mainly lipid metabolism[20] and eicosanoid synthesis.[21,22]

Furthermore, LDs are also involved in inflammatory and infectious diseases.[23] The participation of LDs in infectious disease pathogenesis has been reported for all classes of pathogens, such as viruses,[24,25] bacteria,[26,27] fungi,[28] and protozoa,[29,30] suggesting that

Abbreviations: BCG, bacillus Calmette—Guérin; DENV, dengue virus; FA, fatty acids; HCV, hepatitis C virus; Lam, lipoarabinomannan; LD, lipid droplet; NS, nonstructural; PAF, platelet-activating factor; PAMP, pathogen-associated molecular pattern; PRR, pattern recognition receptor; PV, parasitophorous vacuole; TAG, triacylglycerol.

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LDs participate in the innate and adaptative host immune response to infection. Host LDs may also be exploit as part of the adaptation of pathogens to escape the immune system and as an energy source for intracellular pathogens.[31–33] Here, we review the complex relationship between host LDs and pathogens, highlighting the multiple roles of LDs in pathogen survival and proliferation, as well as in the host's protective response, in the context of host-pathogen interactions.

2 | LD BIOGENESIS IN CELLS OF THE IMMUNE RESPONSE

Although LDs are almost absent in resting leukocytes and other cells of the immune response, increases in the size and number of LDs in cells involved in infectious and inflammatory processes occur so often that LDs have been considered structural markers of inflammation.[6,15] LD biogenesis is a rapid and highly regulated process whose mechanisms and mobilized signaling pathways are dependent on the infectious agent and cell type involved. Of note, LD biogenesis involves multiple steps and de novo LD formation occurs mostly in the ER where the enzymes involved in neutral lipid synthesis are localized providing triacylglicerols and sterol esters for LD formation.[34] Proposed biogenesis models suggest that LDs bud from the outer leaflet of the ER. However, it is still debatable whether at least part of newly formed LDs remains associated with the ER and/or contain remnant ER-derived membranes.[34,35]

Although the molecular mechanisms that govern LD biogenesis during inflammation and infection are still incompletely understood, it occurs as a multimediated process that involves increased lipid uptake, lipolysis inhibition, and new lipid synthesis. Moreover, it has been demonstrated that this phenomenon depends not only on the direct interaction between the pathogen and host cells but also on the indirect mechanisms of a bystander amplification-induced system through bacterial components and/or host-generated cytokines and chemokines.[26,27,36–40]

Pioneer work by Pacheco et al.[36] demonstrates that LDs biogenesis in leukocytes can be triggered by the recognition of pathogen-associated molecular pattern (PAMP) by specific receptors of the innate immunity (PRRs, pattern recognition receptors).[36] Among PRRs described, the TLR family stands out as a well-established molecular pathway for LD biogenesis induction by infectious agents (Table 1).

LPS-induced LD formation in leukocytes was demonstrated to occur through a mechanism largely dependent on TLR4 in cooperation with CD14.[36] Bacterial infection with *Chlamydia pneumoniae* is also capable of inducing foam cell formation[41] in a pathway dependent on TLR2 and TLR4, but not TLR3, as well as the mobilization of the adapter molecules Myeloid differentiation primary response 88 (MyD88) and TIR-domain-containing adapter-inducing IFN-β (TRIF).[42,43] TLRs, mainly TLR2, are essential receptors involved in the recognition of distinct mycobacterial products.[44] Signaling through TLR2 proved to be essential to trigger LD formation in macrophages during purified bacterial wall component lipoarabinomannan stimuli or *Mycobacterium bovis*[45,46] and *Mycobacterium leprae* infection;[38] in this last case, the deletion of TLR6, which is reported to heterodimerize with TLR2, also impaired LD formation not only in macrophages but also in Schwann cells.[26] Although stimulation of TLR2 is essential, it is not sufficient to induce LD biogenesis because zymosan and Pam_3Cys, potent agonists of TLR2, and the nonpathogenic bacterium *Mycobacterium smegmatis* fail to induce these organelles; therefore, other cofactors must be involved.[45,46]

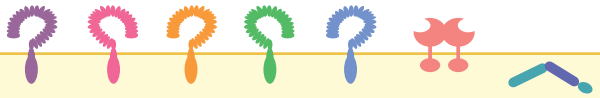
The participation of the TLR in the LD biogenesis is not restricted to bacteria. Fungal infection with *Histoplasma capsulatum*, the causative agent of pulmonary histoplasmosis, has been described to induce an increase in leukocyte LD numbers in a dose- and time-dependent manner, and the TLR2, CD18, and Dectin-1 pathways have been shown to be essential for this mechanism.[28] Similarly, during macrophage infection by the parasitic protozoan *T. cruzi*, the dependence on TLR2 signaling, but not TLR4, for LD biogenesis has been demonstrated.[47] However, the identification of another receptor or downstream signaling pathway involved in the biogenesis of LDs during *T. cruzi* infection remains unknown.

Furthermore, signaling through intracellular PRRs also has been shown to be involved in LD biogenesis. During infection by hepatitis C virus (HCV), activation of NLRP3, a member of the NOD-like receptor (NLR) family responsible for triggering inflammasome activation, was associated with changes in lipid homeostasis observed in infected cells.[48–50] The HCV-activated NLRP3 inflammasome causes the activation of SREBPs that up-regulate lipogenic genes, and these alterations result in the intracellular accumulation of LDs.[48] Since HCV has absolute reliance on host lipids in the various stages of the viral life cycle, LD formation proved to be crucial for liver disease pathogenesis associated with chronic HCV[51,52] (Fig. 2). On the other hand, NLRP3-deficient macrophages infected with *C. pneumoniae* present a significant increase in LD number, probably because activation of the NLRP3 inflammasome is closely associated with capture or use of LDs in chlamydial inclusions in infected BMMs, which is in agreement with the fact that NLRP3 activation favors the growth of *C. pneumonia*.[53]

Downstream pathways involved in LD biogenesis were shown to involve the activation of transcription factors including master regulators of lipid metabolism and nuclear receptors, such as peroxisome proliferator-activated receptors (PPARs), liver X receptor (LXR), SREBPs, and HIF.[42,45,48,51,54–59] Members of subfamily of PPARs, LXR, and SREBPs sense the intracellular lipid environment and modulate expression of key genes in fatty acid uptake, lipid synthesis, lipolytic enzymes, and LD biogenesis.[54,60] Of note, NFκB was shown to counter-regulate LD biogenesis because its inhibition lead to enhanced TLR2-triggered LD formation.[57] The activation of TLR signaling induce the increasing of expressions of several enzymes involved in the synthesis of triglycerides and/or cholesterol ester, such as fatty acid synthase (FASN), diacylglycerol-O-acyltransferase (DGAT-1 and DGAT-2), and acyl-CoA:cholesterol O-acyltransferases (ACAT1 and ACAT2).[61–63] When de novo lipid synthesis is blocked, the biogenesis of LD downstream of TLR activation is severely impaired.[39,47]

Also favoring lipid accumulation, TLR activation has reported the increase in the expression of several receptors involved in

TABLE 1 Receptors of innate immunity involved in inducing LD biogenesis by different pathogens



		TLR2	TRL4	TRL5	TRL6	TRL9	Dectin-1	NLR3	References
Bacterias									
	A. baumannii	•	•						63
	C. pneumoniae	•	•						41-43
	E. coli	•	•	•					63
	K. pneumoniae	•		•					63
	M. bovis BCG	•							45,46
	M. leprae	•			•				26,38
	M. tuberculosis	•							40-113
	P. aeruginosa	•							63
	P.diminuta	•	•						63
	P. vulgaris	•							63
	S. aureus	•							63
	S. epidermidis	•							63
	S. salivarisus								63
Bacterial derivates									
	CpG DNA					•			63
	Flagellin			•					63
	LPS		•						36
	LAM	•							45-46
Virus									
	HCV							•	48-50
Fungus									
	H. capsulatum	•	•				•		28
Parasites									
	T. cruzi	•							47
	S.mansoni	•							100

increased lipid uptake and transport,[57,61,62,64] as well as the decrease in expression of lipolytic enzymes, mainly adipose triglyceride lipase (ATGL).[61,62] The increase in the lipid content in the cells is accompanied by the increase in the expression of LD structural proteins, mainly adipose differentiation-related protein/Perilipin-2 (ADRP/Plin2)[62,65,66] and tail-interacting protein of 47 kD/Perilipin-3 (TIP47/Plin3).[67,68] Moreover, these structural proteins are essential to LDs assembly and biogenesis.[69]

Among these regulators, PPARs have been the most explored during the infectious process. PPAR can directly impact LD formation by modulating ADRP/Plin2 expression, a protein intrinsically associated with LD surfaces with major functions in lipid homeostasis in nonadipocyte cells.[65,70,71] The Plin2 gene has a response element for PPARs, and its expression is positively regulated by their agonists.[72] Additionally, PPARs regulate proteins involved in triggering de novo lipogenesis, including fatty acid synthase, and gene regulatory factors LXR and SREBPs[60] (Fig. 1).

PPARs are expressed by leukocytes, including T cells, B cells, dendritic cells, and macrophages[54,73] and are highly expressed in foam cells within atherosclerotic lesions.[74] Studies have demonstrated that the expression and function of the nuclear receptor are regulated by bacterial components[55,75,76] and are associated with LD biogenesis. Almeida and colleagues demonstrated that experimental infection by *M. bovis* BCG is able to up-regulate the expression and/or activation of PPARγ and induce lipid-laden macrophages, a phenotype that is abrogated when infected cells are pretreated with GW9662, a selective antagonist of PPARγ.[52] All of these mechanisms are under the control of TLR2 signaling because BCG-induced PPARγ expression, LD formation, and TNF-α generation were drastically inhibited in TLR-2-deficient mice.[52,76] However, activation of the TLR2 pathway is not sufficient to induce PPARγ expression because stimulation with the nonpathogenic bacterium *M. smegmatis* may activate TLR2-dependent TNF-α production without an increase in PPARγ expression.[52,76] This finding raises the possibility of the participation of other cofactors

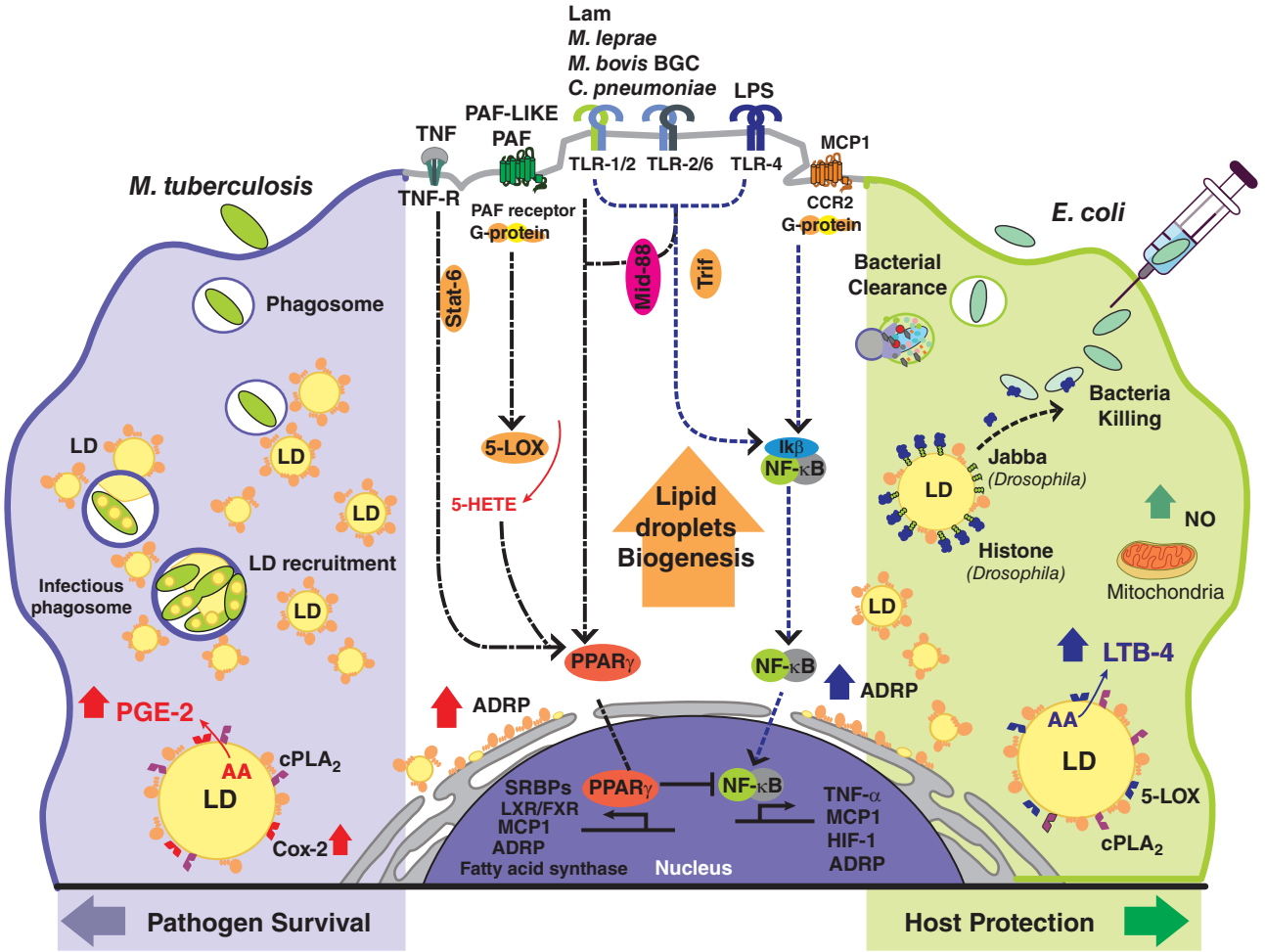


FIGURE 1 **The roles of lipid droplets (LDs) at bacterial infections.** LD biogenesis is a higher regulated process, involving several receptors of innate immunity, including TLR, which recognize bacteria or parts of bacteria. Moreover, several cytokines and lipid mediator molecules induced the LDs accumulations, such as MCP-1/CCL2, hydroxyeicosatetraenoic acid (5-HETE), platelet-activating factor (PAF), and PAF-like molecules. Activation of the receptors of these molecules started a complex signaling cascade that culminates in the activation of peroxisome proliferator-activated receptor γ (PPAR-γ) or NF-κB, which directly or indirectly induce the activation of several lipogenic genes (SRBPS, LXR/FXR, HIF-1, fatty acid synthase) and structural proteins of LDs, such as PLIN2/ADRP. After the induction, bacteria recruit the LDs to the vicinities of the bacteria-containing endosomes. The interaction of LDs with bacteria-containing phagosomes leads to the release of LDs contents, such as cholesterol and triacylglycerol, which serve as a nutritional source for pathogen bacteria survival and proliferation. In addition, LDs are also important players in innate immunity. Host-pathogen interaction leads to the biosynthesis and secretion of inflammatory mediators such as prostaglandin E_2 (PGE_2) through arachidonic acid (AA)-derived cyclooxygenase (COX-2) pathways. PGE_2 may potentially inhibit Th1 response, thus favoring pathogen proliferation. In contrast to LDs recruitment mechanisms to the pathogen benefit, innate immunity actors, such as histones in *Drosophila*, are localized at the LD surface and may act as antibacterial proteins. Besides, LDs are also a site for production of leukotriene B_4 (LTB_4), a pro-inflammatory eicosanoids AA-derivated lipoxygenase (5-LOX) pathways, associated with the pathogen's elimination

in this signaling; indeed, BCG-induced PPARγ expression and LD formation are largely dependent on CD36 activation in association with CD11b/CD18 and CD14 compartmentalized on lipid rafts.[57]

During the infectious process, the observation that LD biogenesis can be triggered in relatively short timeframes and occurs both in cells carrying the infectious agent and likewise in uninfected cells demonstrates that this phenomenon does not depend exclusively on direct interaction between pathogens and the host cell, but indirect mechanisms may amplify this response.[47] In fact, several molecules produced during the inflammatory response act in a paracrine manner, inducing LD formation, including lipid mediators, cytokines, and chemokines.

Platelet-activating factor (PAF) and PAF-like molecules are inflammatory phospholipids recognized by a single G protein-coupled PAF receptor[77] and play an important role in LD biogenesis in leukocytes such as neutrophils[78] and eosinophils.[21,79] Blocking the PAF receptor with an antagonist or inactivation of ligands recognized by the PAF receptor by administration of phospholipase PAF acetylhydrolase significantly inhibits LD formation induced by oxLDL, LPS, or sepsis.[80,81] Studies with pharmacological inhibition and genetically deficient mice show that the downstream pathway behind rapid PAF-induced LD formation in PMNs depends on 5-lipoxygenase (5-LO) activity to form 5(S)-hydroxyeicosatetraenoic acid, as well as subsequent stimulation of protein kinase C and phospholipase C;[78] PAF-induced LD biogenesis

requires new protein synthesis, may be amplified by PPARγ activation, and has an intense crosstalk with MCP-1/CCL2 signaling.[36,78,81,82]

The monocyte chemoattractant protein (MCP-1, also known as chemokine ligand 2 [CCL2]) is a central chemokine in mononuclear cell recruitment.[83] In different models such as saturated fatty acid-[84,85] or oxLDL-rich conditions,[66] leptin stimuli in tumor cells,[86] polymicrobial infection, or LPS-driven inflammatory responses,[37] the increase in MCP-1/CCL2 production occurs in parallel to LD formation. Indeed, MCP-1/CCL2 directly induces a dose-dependent increase in the numbers of cytoplasmic LDs in vitro within resident peritoneal macrophages isolated from naive mice, indicating that its effect occurs through cell migration independent pathways. During sepsis or LPS-induced inflammation, LD biogenesis in leukocytes was virtually absent in MCP-1/CCL2$^{-/-}$ mice.[37] MCP-1/CCL2 was also centrally involved in foam cell formation induced by oxLDL because pretreatment with neutralizing anti-MCP-1/CCL2 inhibited macrophage ADRP/Plin2 expression and drastically reduced the number of LDs.[66] MCP-1/CCL-2 paracrine activity has been shown to induce LD biogenesis through its cognate receptor CCR2, MAP kinase, ERK, and PI3K downstream signaling, and requires the maintenance of a well-organized microtubule network because both microtubule-disrupting and -stabilizing drugs (colchicine and taxol, respectively) have inhibitory effects on LD biogenesis.[37] Although MCP-1/CCL2 produced in the course of BCG infection has a proven role in leukocyte recruitment,[87] it is not essential for signaling of LD formation. Indeed, BCG infection triggered LD biogenesis in MCP-1/CCL2$^{-/-}$ in similar amounts in wild-type mice.[46] This finding suggests that the cell migration may modulate, but is not essential for LD accumulation in leukocytes during inflammation, and redundant LD-triggering mechanism may occur in mycobacterial infections, which is also independent of both TNF-α and IFN-γ.[46] In this context, IL-6, a STAT-activating cytokine, has been described to increase intracellular mycobacterial survival via effects on triglyceride deposition in macrophages. IL-6 treatment potentiated the increase in intracellular LDs driven by *M. bovis* BCG infection and promoted intracellular mycobacterial survival probably by enhancing bacterial access to host triglycerides. These effects were dependent on DGAT1 activation, and DGAT-1 inhibition abolished the ability of mycobacteria to drive LD accumulation and eliminated the ability of IL-6 to promote mycobacterial survival.[88]

3 | LD FUNCTIONS IN INFLAMMATION

Eicosanoids are lipids derived from enzymatic oxygenation of arachidonic acid via the cyclooxygenase (COX) and lipoxygenase (LOX) pathways. In contrast to their precursor, eicosanoids are newly formed and nonstorable molecules.[6,22] Moreover, eicosanoids are signaling lipids that have important roles in both physiological and pathological conditions, such as tissue homeostasis, host defense, and inflammation.[22,89] The compartmentalization of eicosanoid synthetic machinery is a crucial component in the regulation of eicosanoid synthesis and in delineating intracellular and extracellular functional actions of eicosanoids.[89,90] Substantial evidence has demonstrated that LDs are specialized intracellular sites for eicosanoid synthesis, often associated with the inflammatory, infectious, and neoplastic processes.[15,22,23]

In leukocytes, LDs are one of the principle storage sites of arachidonic acid, esterified in phospholipids on the LD monolayer and in triglycerides at LD core from where it can be mobilized by phospholipases or ATGL, respectively.[91–95] Furthermore, LDs compartmentalize the entire enzymatic machinery for eicosanoid synthesis, including phospholipase A2 (PLA_2),[95] activating kinases involved in the arachidonic acid mobilization pathway (ERK1/2, p85, and p38),[95] and all relevant eicosanoid-forming enzymes (COX-1, COX-2, 5-LOX, 15-LOX, 5-LO–activating protein, PGE-synthase, and LTC_4-synthase).[66,79] The presence of all these components causes LDs to be capable of rapid arachidonic acid mobilization to produce prostaglandins and leukotrienes.[21,89,90,95]

During inflammatory and/or infectious stimulation, a significant correlation has been reported between LD biogenesis and improved generation of eicosanoids in leukocytes.[6,15,47] Stimuli that induce or inhibit LD formation also coordinately enhance or inhibit eicosanoid synthesis, respectively, in activated leukocytes in a dose-dependent manner.[22,96] In this context, it has been experimentally demonstrated that LDs are main sites of production of leukotriene C_4 (LTC_4),[66,97] leukotriene B_4 (LTB_4),[37,66] prostaglandin E_2 (PGE_2),[46,47,98] prostaglandin D_2 (PGD_2),[99] and eoxin C_4 (EXC_4)[100] during inflammatory and infectious conditions. Other data further indicate that LDs could be the site of synthesis of lipoxin B_4 (LXB_4)[58] and prostaglandin F2alpha (PGF2α),[58,101] however, they still need validation. Several studies have shown that numerous pathogens stimulate the biosynthesis of PGE_2, which could act as an anti-inflammatory mediator favoring the persistence of the pathogen.[22,96] In this situation, LDs were reported as being a site for PGE_2 generation during infection by *M. bovis* BCG[46] and *T. cruzi*.[47] In both infections, PGE_2 production was reported as permissive to pathogens and probably downmodulate macrophage antimicrobial response.[46,47] Furthermore, PGE_2 not only affects infected leukocytes but may also inhibit Th1 responses, which would favor pathogen proliferation and dissemination.[102] Moreover, LDs in colon cancer cells are active organelles involved in PGE_2 synthesis and may have implications in the pathogenesis of adenocarcinoma of the colon.[98]

In contrast, the synthesis of LTB_4, a pro-inflammatory mediator, has also been reported in LDs during the inflammatory response, such as observed during sepsis or endotoxemia.[37] LTB_4 generation during infection contributes to parasite killing[103,104] through indirect effects mediated by amplification of other inflammatory molecules, mediating the recruitment and activation of effector cells.[105] The balance between the generation of PGE_2 and LTB_4 is central in the immune response.[22,105] As a platform for the synthesis of these lipid mediators, LDs probably play an important role both in the survival of pathogens and in the effective host response to infection, but it is still unclear which events mediate each type of response.

The synthesis of inflammatory lipid mediators on LDs also makes this organelle a central component of the leukocyte response in inflammation. As a site of production of LTC_4, PGD_2, and EXC_4, the LDs

are also intimately involved in autocrine and intracrine signal transduction in immune cells,[89,100] especially in eosinophils. For example, LTC_4 activates an intracrine signal-transducing pathway that mediates secretion of eosinophil granules, including cytokine IL-4.[106] In comparison, PGD_2, also synthesized on LDs, is an autocrine signal for eosinophil activation,[99] probably acting as a signal amplifier through the activation of 5-LOX[99] and 15-LOX.[100] The production of EXC_4, which occurs on eosinophil LDs, has implications in host-pathogen interactions.[100] Schistosoma-derived lipids induced EXC_4 synthesis that activated eosinophils to release TGF-β, an immunomodulatory and pro-fibrotic mediator.[100]

In addition to a site of synthesis of inflammatory lipid mediators, LDs are also involved in other functions during the host response to infection. The presence of the pro-inflammatory cytokine TNF-α and macrophage migration inhibitory factor (MIF) was reported in LDs from leukocytes.[36,107,108] However, the biological implication of the association between TNF-α and LDs remains to be understood. In addition, the association of LDs with other cytokines is still unknown. Recent studies have reported the participation of LDs in the IFN response, both in signaling pathways and in the effectiveness of the response.[11,109] Proteins key to the antiviral virus-inhibitory protein, ER-associated, IFN-inducible (viperin),[31] and antiparasitic (immunity-related GTPase M)[33] activities are observed to be loaded on LDs after IFN stimulation.

4 | LD FUNCTIONS IN BACTERIAL INFECTION

Bacterial pathogens display an efficient set of adaptations that support crucial infection events, including bacterial survival, replication, and host immune evasion.[4,110] For successful infection and replication, numerous bacterial pathogens have evolved many approaches to subvert host cellular functions and metabolism.[4,110,111] A change in host lipid homeostasis and LDs biogenesis upon bacterial infection is highly pronounced in both human and experimental infections[6,36,96,112] (Fig. 1).

The subversion of LDs by pathogenic bacteria to complete their own life cycle has been reported for several intracellular bacteria, such as *M. tuberculosis*,[40,113] *M. bovis*,[46] *M. leprae*,[26] *C. trachomatis*,[114] and *C. pneumoniae*.[42] The inhibition of lipid metabolism and/or interference with LDs homeostasis impact bacterial survival[38,115] and/or replication[116] within the host cells. The LD accumulation during bacterial infection is usually associated with a mechanism to obtain an energy resource from the host, as well as a strategy to escape the immune system through increased generation of eicosanoids.[15,22,29,96]

The presence of foam cells, LD-filled macrophages, is a recurrent feature in mycobacterial infections.[38,40,45] The formation of foam cells is a process apparently critical for bacterial persistence in the host and for the pathogenesis of mycobacteria.[39,113,117] For successful infection and persistence of *M. tuberculosis*[115] and *M. lepra*,[39] host lipid molecules are essential. In *M. tuberculosis* infection, the presence of foam cells can be found in both early infection stages[113] and granulomas.[40] In addition to the formation of foam macrophages, during *M. lepra* infection, the same phenotype has also been reported in Schwann cells.[39]

Usurpation of fatty acids released from the host triglycerides stored in LDs is a vital source of energy for mycobacteria, and the storage of fatty acids in the form of triglycerides in bacterial LDs could be linked to the dormancy and reactivation of *M. tuberculosis*.[40,113] Cholesterol is another lipid essential to mycobacterial survival.[118,119] *M. tuberculosis* has the capacity to use cholesterol as an energy source, which is important during latent-phase infection.[119,120] Despite being essential for building blocks for *M. lepra* growth and survival, cholesterol metabolism is not coupled with energy production.[118]

During the mycobacterium infections, the LDs are redistributed or recruited to vicinity of bacterium-containing phagosome.[115,121] Interfering with cytoskeletal function affects not only the impairment of recruitment of host LDs to the phagosome but also the decline of *M. leprae* survival in infected cells.[39] This process enables the capture of lipids by mycobacteria (Fig. 1), suggesting that the LDs are tightly apposed to phagosomes and that there is the physics interaction between LDs and phagosomes.[40,46] With the continuation of infection, mycobacterial-containing phagosomes engulf cellular LDs and this process, which is reminiscent of autophagy, resulted in the transfer of host LDs into bacteria.[40,115]

On the other hand, Knight et al.[58] proposed that LD formation in macrophages might not be an *M. tuberculosis*-induced process but could be a glycolytic programming event dependent on IFN-γ and HIF1-α signaling in murine macrophages. Additionally, in this same work, IFN-γ-induced LDs were an important platform for the production of a broad range of host protective eicosanoids, especially LXB_4 and PGE_2, improving the macrophage immune response.[58] However, the presence of IFN-γ is not sufficient to induce LDs accumulation, requiring a second signal via TLR2,[58] which does not exclude the *M. tuberculosis* as a possible inducer of LDs biogenesis. Interestingly, in this system, *M. tuberculosis* was able to acquire host lipids in the absence of LDs but not in the presence of IFN-γ-induced LDs.[58] Although it seems contradictory to current literature, the induction of LDs as a host response cannot be underestimated, which suggests that LD is an initial protective organelle to the host but some pathogens may have co-opted it over pathogen-host co-evolution.

LD accumulation has also been observed in *C. trachomatis* infection of epithelial mucosal cells.[114,116] Neutral lipids from host LDs appear to be crucial for bacterial propagation of *C. trachomatis*.[116] During *C. trachomatis* infection, LD accumulation inside the chlamydial inclusion[116] was reported. Impairment of lipid metabolism by triacsin C treatment and the consequent inhibition of LD biosynthesis also reduced chlamydial proliferation and the size of the chlamydial inclusion.[116] In a mouse model, incorporation of LDs into the bacterium-containing vacuole has also been observed in infection by *C. muridarum*.[122]

In contrast to other pathogens, *C. trachomatis* induces the translocation of an entire LD from the host cytoplasm into the lumen of the chlamydial inclusion in a process resembling endocytosis.[114] The full

molecular mechanism of capture and translocation of an LD into the chlamydial inclusion remains to be elucidated; however, experimental data suggested that the chlamydial protein Lda3 plays a major role in this organelle sequestration.[114] Lda3 has tropism for both LDs and the inclusion membrane, which suggests that it can mediate the formation of links between them. Moreover, the overexpression of Lda3 leads to the redistribution and replacement of ADRP/Plin2 from the surface of host LDs.[114]

Although LDs are usually seen only as a structure favoring the survival of pathogenic bacteria, several studies have demonstrated the presence of LDs in pro-inflammatory environments.[36,63,123] In sepsis, a life-threatening organ dysfunction caused by a dysregulated host response to infection,[124] changes in lipid metabolism are often observed in the form of LD accumulation in several cell types both in vivo and in vitro, including in leukocytes from septic patients.[36] The LD accumulation in the inflammatory microenvironment was also reported during natural infection of *Vibrio cholerae* serogroups O1 and O139.[123] LD accumulation induced by *V. cholerae* infection was only in mucosal mast cells and not in polymorphonuclear neutrophils.[123] Nicolaou et al.[63] reported that both Gram-negative (*Acinetobacter baumannii*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Pseudomonas diminuta*, and *Proteus vulgaris*) and Gram-positive bacteria (*Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Streptococcus salivarius*) induced the intracellular accumulation of cholesterol ester in macrophages, probably in the LDs, which is a characteristic phenotype of the foam cells. In this work, it was shown that the cholesterol ester accumulation induced by bacteria or PAMP was a highly regulated process mainly involving TLR-2, TLR-4, and TLR-5.[63] Furthermore, these TLRs not only induced lipid storage but also promoted the secretion of the pro-inflammatory cytokine IL-6.[63] Curiously, one of *P. aeruginosa* multiple virulence factors is the type III secretion toxin ExoU, which has cytosolic PLA2 activity[125] with a strong implication in increasing prostaglandin production,[126,127] promote in macrophages infected a significantly decreased LD contents with the release of free AA and PGE_2.[127] This suggests that part of the pathogenic mechanism of toxins ExoU from *P. aeruginosa* could be the mobilization host lipids from LDs.[112] Taken together, these findings suggest that LD accumulation could participate in inflammatory amplification during bacterial infection.

Additionally, van Manen et al.[91] suggested that LDs could contribute to increased production of reactive oxygen species through the activation of NADPH oxidase. For superoxide production, NADPH oxidase seems to require arachidonic acid stimulation.[128] Through a transient LD-phagosome association, LD release of arachidonic acid near the phagosome could be used to locally activate NADPH oxidase and/or to facilitate phagosome maturation.[91] In both cases, the LDs could contribute to the elimination of pathogens.[91] Moreover, Fock et al.[129] reported that mitochondrial reactive oxygen species contribute to the LPS-induced shift of lipid metabolism and LD biogenesis in epithelial cells.[129] Together, these results suggest that there is probably a close crosstalk between LDs and oxidative stress in infection, which has not yet been fully explored, but which may have a profound impact on the pathogen-host interaction.

An important paradigm shift was the discovery of antibacterial function by the LDs reported by Anand et al.[32] In vitro assays show that LDs purified from *Drosophila melanogaster* embryos possess in vitro antibacterial activity against *S. epidermidis* and *E. coli*. In this same work, it was verified that this antimicrobial response was due to the protein content of this organelle, mainly due to the action of histones.[32] Despite being a cationic protein canonically involved in the formation and maintenance of nucleosomes,[130] histones are cytotoxic in vitro and in vivo when located in the extracellular environment, or when in excess in the cytoplasm, furthermore, they have a strong ability to kill bacteria[130–132] (Fig. 1). Compartmentalization of histones on LDs was first detected during oogenesis[18] and involved the participation of the LD protein Jabba, which interacts physically with histones to recruit them to the organelle and keeps them stored through a weak electrostatic interaction.[133] Mutant fly embryos lacking Jabba have drastically reduced histone stores, and when challenged by intraembryonic inoculation with *E. coli*, they lost the capacity to control bacterial infections and showed a low survival rate.[32] The role of histones in antibacterial activity seems not to be restricted to the embryonic period. Jabba mutant adult flies, when inoculated with the intracellular bacteria *Listeria monocytogenes*, presented higher and faster mortality than did the wild-type flies.[32]

The presence of histones in LDs seems not to be limited to insects. LDs isolated from the livers of mice challenged with LPS showed increased loading of histone H1.[32] The identification of histones in LD proteomic analyses of rat sebocytes[134] and human macrophages[135] has been reported. Localized histones as protective proteins on LDs against intracellular bacteria may indicate the existence of a new type of conserved innate immunity, but the absence of proteins homologous to *Drosophila* Jabba in mammals[133] leaves the mechanism and nature of histone-LD interactions still unknown in mammals.

The presence of LD in host immune cells during bacterial infection is a recurrent phenomenon in the literature. Although great advances were made in recent years to characterize the mechanisms of biogenesis and functions during infection, several issues remain open. Collectively, LD formed during bacterial infection involves multimediated and specific mechanisms that vary according to both the pathogen and the host cells involved. The functional outcome of the increased LD accumulation may favor the pathogen as the described subversion of this organelle by intracellular pathogenic bacteria as part of the evasion mechanism of the system or as an energy source; or may act pro-host immune response. Future studies are in need to better characterize the specificities of this complex interactions according to the different infections.

5 | LDs AND VIRUS INFECTION

Viruses are obligate intracellular pathogens that subvert host metabolism and cellular structures for viral replication and assembly.[49,136] In the cytoplasm of the cell, all positive-stranded RNA (+RNA) viruses of eukaryotes promote an extensive modification of the host membrane web, transforming them into a

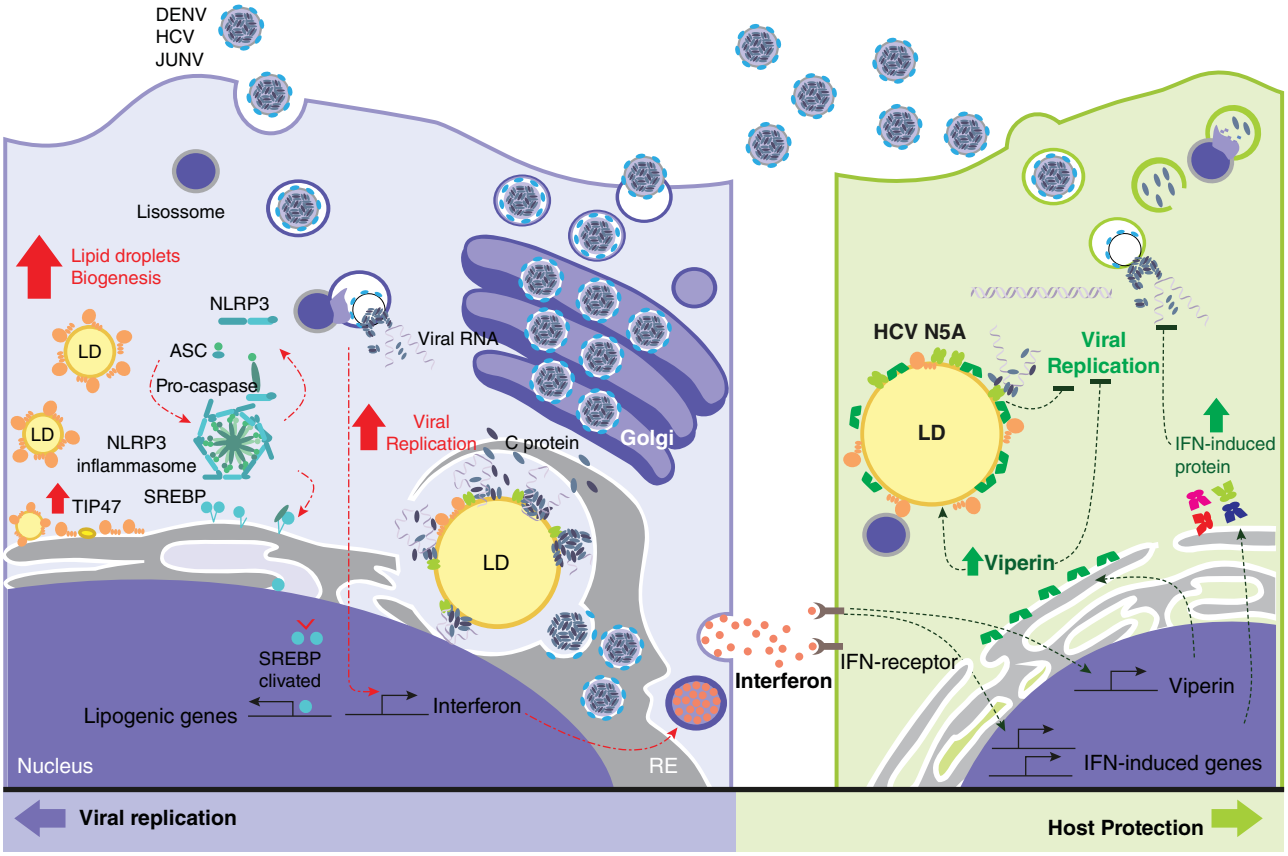


FIGURE 2 **The roles of lipid droplets (LDs) at viral infections.** Lipid metabolism and LDs are important components in the positive strand (+) RNA viral cycle, such as flavivirus members. During viral infection, there is the induction of LD in a process involving the activation of NACHT, LRR, and PYD domains-containing protein 3 (NLRP3) inflammasome, which cleaved the sterol regulatory element-binding proteins (SREBPs), activating the lipogenesis genes and the structural LDs proteins, such as PLIN3/TIP 47. After LD accumulation, it can be a platform for viral replication and/or assembly of several viruses, such as hepatitis C virus (HCV) and dengue virus (DENV). On LDs, the presence of HCV core (C) protein and NS5A complexes has been reported, together with the LD-associated proteins PLIN3/TIP47, which facilitate the interaction of LDs with specialized areas of the ER-containing NS5A. After assembly, the pro-virus goes to the lumen of the endoplasmic reticulum (ER) and the complex Golgi until they are released to the extracellular environment. In contrast, the presence of LDs could be required for an effective early innate response to viral infection, which is mainly related to IFN response. IFN signaling activates hundreds of genes (IFN induced), vital in the host response mechanism to viral infection, including viperin. Viperin is a potent antiviral protein that accumulates in ER and LDs, inhibiting the virus replication

specialized microenvironment that is thought to support viral RNA synthesis.[136–138] In this process, strong evidence has demonstrated that lipid metabolism and LDs are important components in the +RNA viral life cycle, either as one of the sites for viral replication and/or assembly or as a source of energy through autophagy[96,139] (Fig. 2).

Several (+)RNA viruses use host LDs at different steps of their life cycle, such as reovirus,[140] rotavirus,[141] norovirus,[142] Junín virus,[143] and poliovirus,[10] as well as various members of the Flaviviridae.[24,25,144] These viruses manipulate lipid metabolism for efficient viral morphogenesis, and inhibition of lipid metabolism and/or interference with LD homeostasis decreases viral replication and/or assembly.[25,52,143]

Although the replication of flaviviruses is associated with the endoplasmic reticulum, LDs are also an important component of viral morphogenesis.[24,25,52,145] In this context, several viral proteins have been reported on LDs, including nonstructural proteins (NS) linked to replication, such NS4B,[146] NS5A, and NS3 protein[144,145] of HCV, as well as the capsid core proteins of HCV,[147,148] GB virus-B,[149] and dengue virus (DENV).[24,25,150] In addition to the presence of viral proteins on LDs, the presence of HCV viral RNA was reported in this organelle.[52] Furthermore, proteomic research reported the presence of ribosomes and chaperones on LDs,[151] which suggest that the LDs may hypothetically be capable of supporting viral replication and assembly independent of the ER, but this has not been proven experimentally yet.

The anchoring of the viral proteins in LDs involves the presence of an amphipathic α-helix.[25,52,152] For the DENV core protein, 2 leucine residues (L50 or L54) in the α2 helix are essential for LD association.[25] In comparison, for HCV and GB virus-B core proteins, the motif essential for LD anchoring contained proline residues in the α-helix. In addition to the intrinsic structure of the viral proteins, it has also been proposed that several host proteins could mediate the anchoring of viral proteins onto LDs. In this context, LD-associated protein PLIN3/TIP47 is an important mediator of anchorage of HCV NS5A and core protein[68,145] and the DENV core protein[24] on LDs. HCV core and

NS5A proteins interact with DGAT1 and depend on DGAT1 activity for access to LDs.[153,154] The physical association of cell factor Rab18 with HCV NS5A promotes the interaction between LDs and sites of viral replication.[155] The use of a noncanonical function of the host trafficking system GBF1-Arf1/Arf4-COPI pathway for capsid accumulation on LD was also reported for DENV.[156]

The localization of the viral core protein and NS proteins onto LDs seems to be required for successful production of infectious viral progeny. The presence of HCV viral protein to LDs is a higher coordinated process, each step being essential for the next step in order to form the replication complexes around the NS5B RNA-dependent RNA polymerase that copies the viral genome.[52,157] The first HCV protein translocated from the ER to the LD surface is the core protein, which in turn assists in recruitment of the NS5A and this in turn recruit other viral NS proteins to the LD surface.[52,157] Mutations of HCV core and NS5A proteins, which failed to associate with LDs, reduced the production of infectious viruses, probably because of the impaired replication complexes.[52] The same phenomenon was observed for DENV, where mutations in the core protein that prevented anchoring onto LDs resulted in impaired viral replication and assembly.[25] In addition, HCV core protein induced the accumulation of LDs,[52] and steatosis is a phenotype frequently observed in HCV-infected patients.[49,50,139] These data support the role of LDs as an important platform for viral morphogenesis. However, the mechanism by which LDs gain or lose viral proteins is still an open question, as well as the possibility of some viral proteins arriving from LDs during the formation of this organelle in ER.

In addition to flaviviruses, rotaviruses also co-opt LDs for their replication. In rotavirus infection, LDs are associated with components that physically resemble viroplasms, the structure described as "factories" of virus production.[141] The LD structural proteins (PLIN1 and PLIN2/ADRP) colocalize with the rotavirus nonstructural proteins NSP2 and NSP5 and with the structural proteins VP1, VP2, and VP6.[141] The NS3 protein of human norovirus (huNoV) was tightly associated with LDs and induced convoluted membranes, structures responsible for viral replication.[142] Moreover, the μ1 outer capsid protein of reoviruses was also reported on LDs.[140]

Notwithstanding being an important viral replication site, LDs can also be an important energy and building block source for viral replication and assembly. DENV induced proviral, autophagy-dependent processing of LDs (lipophagy) in infected cells.[158,159] The induction of autophagy is another mechanism by which viruses can alter cellular lipid metabolism, by increasing cellular β-oxidation, which generates ATP and can be used in viral replication and assembly.[160–162] On the other hand, during poliovirus replication, the LDs are used as building blocks for the formation of structural development of poliovirus replication organelles. The LD's neutral lipids hydrolysis and re-route from triglyceride to phosphatidylcholine synthesis, and these are used in the formation of a viral replicative organelle-like structure to replication.[10] Despite of this remodeling membranous not be essential for viral RNA replication, this process seems be important for protection of virus replication from the host antiviral response, mainly during multicycle replication of poliovirus.[10]

Despite the participation of LDs in (+)RNA virus replication and assembly, the importance of this organelle for the other viral classes is still unknown. The only exception is polyomavirus BK, a DNA virus whose agnoprotein was reported on LDs.[163] The biological relevance of these associations remains to be determined, but these findings suggest the possibility that other virus classes may use LDs as a platform for viral particle assembly.

LDs are not always unfavorable to the host during viral infections. The presence of LDs could be required for an effective early innate response to viral infection, mainly related to type I and III IFN responses.[164] In response to viral infection by HCV, viperin was the first protective protein reported to be loaded onto LDs.[31] The antiviral protein viperin is one of the hundreds of genes regulated by the cell-signaling proteins and master regulators IFNs in response to viral infection.[165–167] The IFN-induced genes are vital in the host response mechanism to viral infection.[168,169]

Viperin has a broad and potent antiviral activity,[168,169] however the exact mechanism of viperin antiviral action remains unknown, but several indications suggest that viperin can inhibit different viruses by different pathways.[109,166] Structurally, viperin's amino-terminal amphipathic α-helix seems to be important for full antiviral activity because it is involved in protein subcellular localization[31] and physical interaction with proteins essential to viral replication.[31,143,170] Tagged proteins inhibited by viperin have been reported, including HCV NS5A,[31] DENV NS3,[170] Junín mammarenavirus N protein,[143] and probably chikungunya nsP2,[171] which are important proteins in viral RNA transcription and replication.[172–174] Furthermore, viperin seems to induce lipid raft disturbance and, as a consequence, impairment of membrane localization of viral proteins and inhibition of virus release.[175,176]

The mechanism for subcellular targeting of viperin via its α-helix to the LDs is similar to that described for the HCV NS5A viral protein, indicating that part of viperin's antiviral activity may be mediated by the subcellular localization of the protein,[31] probably acting as part of localized antiviral tactics to limit viral propagation. The viperin antiviral pathway at the LD level was also proposed for JUNG virus[143] and probably for other flaviviruses.[31] However, viperin anchorage onto LDs is dispensable for DENV inhibition.[170]

Notwithstanding, the interaction of LDs and viperin can be associated with another side of viperin's antiviral activity in addition to direct viral suppression. Saitoh et al.[177] showed strong evidence that viperin acts as a regulator for pattern recognition receptor-mediated innate immune responses, facilitating TLR7- and TLR9-mediated production of type I IFN in plasmacytoid dendritic cells. In this system, the LDs act as scaffold for TLR7 and TLR9 signaling pathways, suggesting that viperin recruits IRAK1 and TNF receptor-associated factor 6 (TRAF6) in a stimulation-dependent manner.[177] The compartmentalization IRAK1 and TRAF6 on LD facilitates the ubiquitination of IRAK1 by TRAF6, which results in the IFN regulatory factor 7 mediated induction of type I IFN.[177] In this context, the localization of viperin on the LD appears to play a key role in the regulation of host defense responses to viruses.[177]

The antiviral activity of viperin against infection by herpesvirus, flavivirus, alphavirus, orthomyxovirus, paramyxovirus, rhabdovirus,

retrovirus, and picornavirus has been confirmed.[109,168,169,171,178] For most of these viruses, the mechanism by which viperin restricts replication is not fully clear. In at least some cases, enrichment and compartmentalization of viperin on the LD surface may participate in the inhibition of viral replication.[13,166]

6 | LDs AND PROTOZOAN INTERACTIONS

Parasite protozoans have complex molecular machinery to interact with their host cell in order to evade and manipulate the immune response.[179–181] Upon entering the host target cell, the parasites are internalized within the parasitophorous vacuole (PV), a plasma membrane–derived vacuole where the parasite survives and multiplies[179,182] (Fig. 3). Overall, LD biogenesis during protozoan infection occurs in parallel with PV formation and progression in the host cell cytoplasm.[15,180] The accumulation of LDs in infected cells has been reported for several parasites, such as *Trypanosoma cruzi*,[135,183] *Leishmania amazonensis*,[184] *Leishmania major*,[185] *Leishmania infantum*,[186] *Plasmodium chabaudi*,[187] *Neospora caninum*,[61] and *Toxoplasma gondii*.[29] During parasite infection, LDs are usually associated with sustaining successful parasite replication within the PV[102,182] (Fig. 3).

The mechanisms involved in LD accumulation during parasite infection are not yet fully understood. Like other pathogens, some studies reported the participation of TLR in parasite-induced LDs, as the case of TLR-2 in the *T. cruzi* infection, which is amplified by the uptake of apoptotic cells in a mechanism dependent on integrins and TGF-β synthesis.[47] Moreover, the activation of TLR-1 and TLR-2 by *Leishmania infantum* lipophosphoglycan induced LDs accumulation in association with PPAR-γ expression.[188] On the other hand, LDs biogenesis was related to dysregulate host metabolism by the subversion of host mTOR and JNK signaling in the *T. gondii* and *N. caninum* infection.[61] Furthermore, *T. gondii* promotes the expression of some triglyceride synthesis genes and lipid transporters, and inhibits the expression of lipolytic genes, especially ATGL, favoring the LD accumulation in the host cell.[61] Several parasites lost the ability to synthesize all lipids essential for their survival, requiring the supply of lipids from the host cell, mainly cholesterol.[182] For several protozoan parasites, they rely on host LDs and their lipolytic enzymatic activities to survive and proliferate.[47,61] LDs are frequently observed around and within the PV.[180,189] The *T. gondii* PV is able to access host lipids by intercepting and engulfing LDs.[190] However, the mechanism of how protozoans acquire the host's lipids is not yet fully understood.

Parasite cells have their own LDs,[61,101,102] as well as those of the host cells, and parasite LDs are dynamic structures able to respond to host interaction and inflammatory events.[102] Moreover, parasite LDs were also reported as being a platform of compartmentalization of the eicosanoid pathway.[101,102] In Leishmania, the presence of PLA_2 and prostaglandin $F_{2\alpha}$ synthase on parasite LDs has been identified.[101] In addition to the presence of PGE synthase on LDs, the accumulation of arachidonic acid and PGE_2 formation on LDs was also reported in *T. cruzi*.[102] The production of inflammatory mediators by parasite LDs suggests that this organelle participates in an elaborate form of evasion of the immune system,[101,102] and it is even suggested that parasite LDs could be classified as a mechanism of pathogenicity.[101]

A recent result connects the antiparasitic response in the presence of LDs. Immunity-related GTPase M proteins are small IFN-inducible GTPases[33,191] and part of a complex cellular system for recognition of its own structures. Irgm3 accumulates in "self" organelles, including LDs, but not in the PV of the bacterial pathogen C. *trachomatis* or the protozoan pathogen *T. gondii*.[33] Although Irgm3 is required for resistance to *T. gondii*[192] and *L. donovani*[193] infections in mice, the roles of the interaction between Irgm3 and LDs in the elimination of the pathogen remain uncertain. It has been suggested that this interaction may be related to blockade of recruitment of LDs by the parasite or even participation of this system in antigen (Ag) presentation.[11,182] Furthermore, it remains uncertain whether LD recruitment favors parasite survival or a host cell defense mechanism (Fig. 3).

7 | LDs AND ANTIGEN PRESENTATION

The first observation of LDs in dendritic cells was reported by Steinman and Cohn,[194] which describes the morphology of dendritic cells from peripheral lymphoid organs. More recently, an increase in the number of LDs in dendritic cells has been described during infection by *Leishmania amazonensis* or *Nocardia brasiliensis* and cancer.[185,195–197] LDs have been described to interact with several organelles and structures within cells, including phagosomes,[91] autophagosomes, and the proteasome.[12] These results suggested that these lipid-rich organelles could be involved in cellular processes related to Ag presentation and immunity.

Dendritic cells are a highly specialized subset of APCs that have an important role in the initiation and maintenance of the adaptive immune response and are capable of stimulating immunologically naïve T cells. Dendritic cell activation involves capturing and processing Ags for the stable presentation of Ag-derived peptides in the context of MHC class I and II proteins, leading to the induction of the expression of chemokine receptors, cytokines, and co-stimulatory molecules.

Under conditions of stimulation of dendritic cell, TLR-ligands IFN-γ, and saponin-based adjuvants are also able to increase lipid content.[191,198,199] Bougnères et al.[191] have shown that LDs are involved in phagosome maturation and cross-presentation via MHC-I in IFN-γ-stimulated dendritic cells. In that work, it was observed that LDs co-localized with the Irgm3 GTPase, which interacts with PLIN2/ADRP and is essential for LD biogenesis. They observed that dendritic cells from Irgm3-knockout mice are impaired for accumulation of LDs and are defective in cross-presentation efficiently, similar to what was observed in PLIN2/ADRP-deficient dendritic cells. This event seems to be direct effect of absence of LDs because neither PLIN2/ADRP-deficient nor Irgm-3-deficient dendritic cells had no dysfunctionality on cell-surface phenotype, on phagocytic ability, on

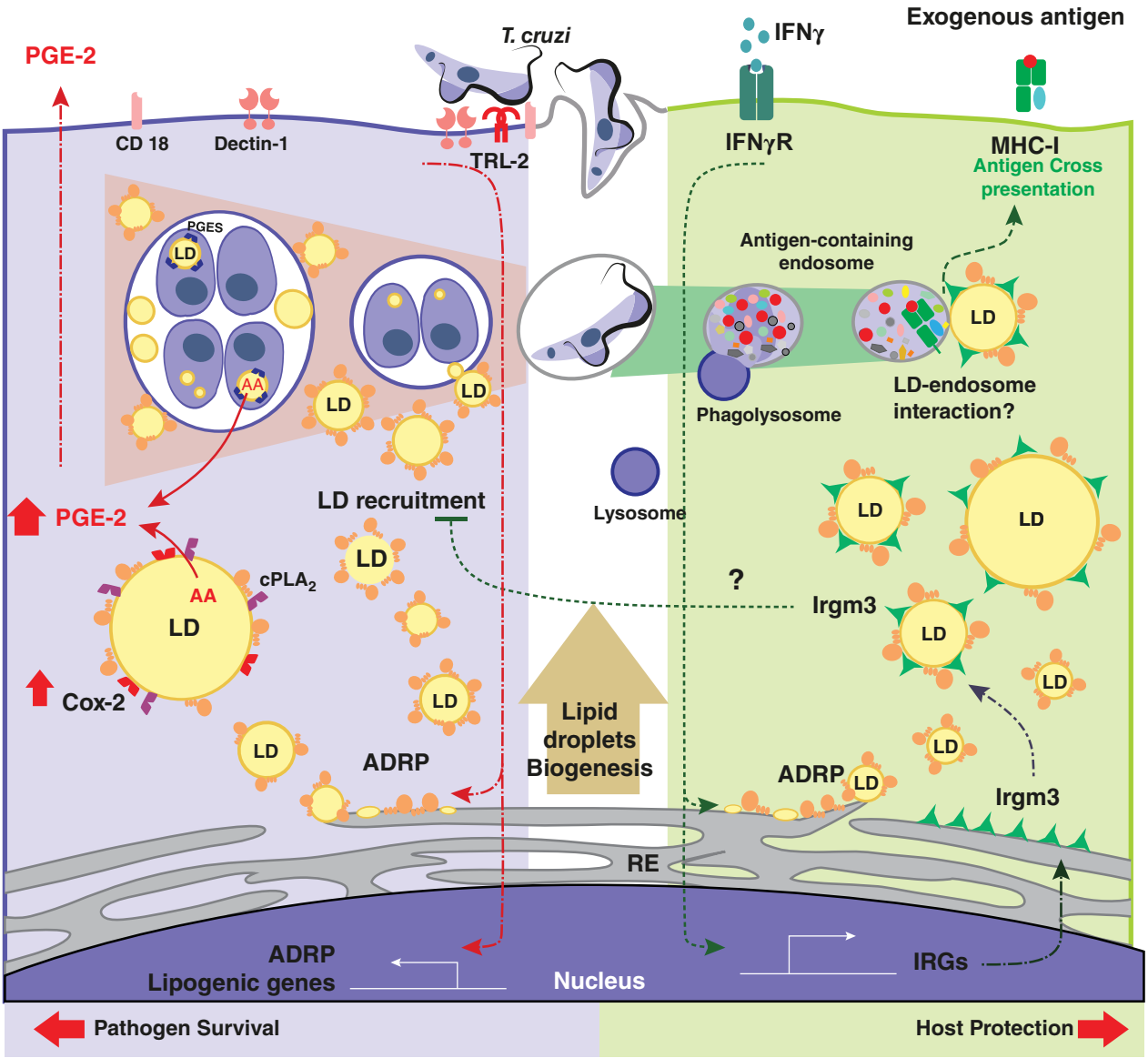


FIGURE 3 **The roles of lipid droplets (LDs) at parasite infections**. In protozoan parasite infections, innate receptor, mainly TLR and co-stimulatory receptors (CD18 and Dectin-1), induced the expression of several genes involved in liponeogenesis, including LDs structural proteins, such as adipose differentiation-related protein (ADRP). LDs are formed in the ER and accumulate in the cytoplasm. The interaction of LDs with phagosomes containing parasites leads to the discharge of LD contents, such as cholesterol and triacylglycerol, which serve as a source of lipids for parasite growth. LDs are also important players in innate immunity. Host-pathogen interaction leads to the biosynthesis and secretion of inflammatory mediators such as prostaglandin E_2 (PGE_2) through arachidonic acid (AA)-derived cyclooxygenase (COX-2) pathways. PGE_2 might favor pathogen proliferation. In addition, parasite LDs are also able to produce PGE_2 through a parasite PGE synthase (PGES). On the other hand, the activating INF-γ pathway induced the expression of Irgm3 (an immunity-related GTPase [IRG]). The IRGM3 accumulated on LD surface and might act as antiparasitic protein. It has been suggested that this interaction may be related to the blockade of recruitment of LDs by the parasite or even the participation of Ag cross-presentation via major histocompatibility complex I (MHC-I)

the ability to present peptide to CD8+ T cells, or on dendritic cell maturation[191] (Fig. 3). Moreover, dendritic cells with an increased lipid content were more competent for Ag cross-presentation.[191] In line with that, stimulation with immune stimulatory complexes containing saponin-based adjuvants, cholesterol, and phospholipids induces the biogenesis of LDs in dendritic cells in parallel to cross-presentation of Ags. Furthermore, genetic and pharmacological blockade of LD biogenesis inhibit Ag cross-presentation induction by saponin-based adjuvants, in vitro and in vivo in a tumor ablation model.[199]

Other studies have correlated lipid content with Ag presentation by dendritic cells. Ibrahim et al.[202] demonstrated that two different dendritic cell populations can be distinguished by lipid content in mouse and human livers, one with high and another with low lipid content. Moreover, the proportion of these 2 populations of dendritic cells in the liver was dependent on states associated with the lipid content of hepatic microenvironment.[200] They showed that dendritic cells with high lipid content presented an activated and immunogenic phenotype and were more effective in activating CD4 and CD8

T cells both in vitro and in vivo when compared to dendritic cells with low lipid content of same tissue.[200] Adoptive transfer of high-lipid dendritic cells delayed tumor progression by activation of cytotoxic T cells. Moreover, the pharmacological inhibition of fatty acid synthase inhibited the cross-presentation and activation of CTL CD8 T cells in vivo.[200] This effect was probably because high-lipid dendritic cells expressed elevated levels of TLRs and co-stimulatory proteins, presented a higher capacity to capture Ags, and produced higher levels of inflammatory cytokines (IL-1β, IL-6, IL-8, and IL-17α) and chemokines (IP-10, KC, MIP-1α, MIP-1β, MCP-1, and RANTES) when compared to low-lipid dendritic cells.[200] These cells also activated NK and NK T cells, suggesting that LDs could also be involved in nonclassical MHC Ag presentation.[200] Likewise, the pharmacological inhibition of LDs formation in LPS-stimulated dendritic cells inhibited cell activation, expression of costimulatory proteins, and pro-inflammatory cytokine production.[198]

In addition to its positive role in the induction of cross-presentation, other data indicate that this process is not only dependent on the presence of LDs but also on other factors that have the capacity of cross-presentation of dendritic cells. Some authors demonstrate in cancer models an opposite correlation between LD induction and Ag presentation. It was observed in murine lymphoma that lipid-enriched dendritic cells are not able to induce CD4 T cell proliferation by the reduction in the expression of co-stimulatory molecules and in cytokine production (IL-12, IL-1, and IFN-γ).[197] Accordingly, it was also demonstrated that lipid-enriched dendritic cells from tumor-bearing mice have a reduced capacity to process and present Ags to T cells, displaying a tolerogenic phenotype. Moreover, the pharmacological inhibition of lipid metabolism reduced dendritic cells containing lipids in tumor-bearing mice and restored their capacity to stimulate T cells.[196]

Dendritic cells incubated with tumor explant supernatants accumulate oxidized lipids, which correlate with the down-regulation of cross-presentation. Lipid peroxidation significantly reduced the ability of dendritic cells to stimulate CD8 T cells due to a reduction in MHC-I loaded with exogenous peptides. It is important to note that lipid peroxidation did not alter the expression of MHC-I molecules or endogenous Ag presentation.[201] This work suggests that not only the presence of LDs in dendritic cells but also their composition may be involved in LD function in the modulation of immune responses. In support of this finding, Veglia et al.[202] reported that oxidized lipids stored in LDs can inhibit cross-presentation in dendritic cells in cancer, indicating that not only the type of lipids but also the oxidative state of these in LDs has implications in antigenic presentation.

Ibrahim et al.[200] demonstrated that high lipid-content dendritic cells presented elevations in phospholipids and triglyceride levels; conversely, cholesterol and cholesteryl esters were not elevated. Accordingly, it was observed that increased levels of saturated fatty acids, such as palmitic acid, reduce MHC-I surface expression and the rate of APC-T lymphocyte conjugation.[203] Thus, LD accumulation of TAG enriched in saturated and or oxidized fatty acids may also play an indirect role in regulating MHC-I expression.[196]

Published data suggest that lipid accumulation in dendritic cells is due to an increase in the capture of lipids from the microenvironment, mainly mediated by the scavenger receptor Msr-1. It has been demonstrated that IL-17 stimulation increases the expression of Msr-1 and other genes related to lipid metabolism, increasing the number of LDs. However, IL-17 stimulation did change the expression of MHC proteins.[204] Similarly, the accumulation of TAG in dendritic cells stimulated with tumor explant supernatants was dependent on its uptake mediated by Msr-1, which was increased in dendritic cells from tumor-bearing mice. In this work, the authors showed that dendritic cells generated from Msr-1$^{-/-}$ mice failed to accumulate lipids after transfer to tumor-bearing recipients and were more effective in T-cell activation.[196] In addition, Msr-1-deficient dendritic cells showed a more mature phenotype.[205] In the absence of Msr-1, tumor-derived factors failed to inhibit Ag cross-presentation by dendritic cells, supporting the possible role of lipid uptake in the negative modulation of dendritic cell function during cancer.[201]

Several pathogens are able to down-regulate Ag presentation to escape the host immune response. It would be important to further elucidate whether these differences in lipid composition and function are directly related to disease mechanisms and could be modulated to favor the host immune response. In addition, defects in the ability to present Ags or modifications in the function of dendritic cells can lead to susceptibility to infections and cancer, and therefore especially in this context, the role of LDs needs to be further investigated, as well as the participation of the microenvironment in this process.

8 | FINAL REMARKS AND PERSPECTIVES

Innumerous intracellular pathogens co-opt host LDs to complete their own lifecycle, using LDs as an energy resource, a platform of assembly or part of their mechanisms to escape the immune response. In addition, LDs participate in several central events in the innate and adaptive immune response, both as a platform for the production of inflammatory lipid mediators and in the response to IFN. In recent years, the presence of LDs during the infectious process has ceased to be seen only as a lipid source organelle for pathogen proliferation and has started to be reported as an important organelle involved in different aspects of the host-pathogen interaction. However, critical questions remain about the formation and the multiple functions that LDs play in infectious diseases. Further investigations should help us to decipher the full range of LD functions in host protective immune response as well as to better understand pathogen-specific mechanisms evolved to take advantage of LDs for their survival and the persistence of infections. In addition, LDs are emerging as attractive target candidates for therapeutic intervention in infectious diseases that progress with increased LD accumulation. Future studies will need to include the development of selective LD inhibitors. Moreover, the safety characterization of LD inhibition is required, as lipid accumulation within LDs may act as a protective mechanism in lipid homeostasis against cellular lipotoxicity.

Take home message

Lipid droplet biogenesis and function

- Increased LDs numbers in leukocytes and other cells are observed in bacterial, viral, fungal, and parasitic infections.
- Pathogen-triggered LD biogenesis is a multimediated process that involves increased lipid uptake, lipolysis inhibition, and new lipid synthesis.
- Innate immune receptors and nuclear receptors play important roles in infection-driven LD biogenesis.
- LDs compartmentalize the eicosanoid enzymatic machinery and are sites of eicosanoid production.
- LDs are a central immunomodulator organelle, both for the pro-inflammatory and anti-inflammatory response.

Lipid droplets in pathogen survival

- Virus may use LDs as viral replication and assembly platforms.
- Intracellular bacteria and protozoa use LDs as a nutritional source for survival and replication.
- Intracellular bacteria and protozoa can induce production of PGE_2 on LDs as part of their mechanism of immune response evasion.

Lipid droplets in the host protection response

- Proteins key in antiviral (viperin) and antiparasitic (IRGM) activities are loaded onto LDs after IFN stimulation.
- LDs can store histones, exhibiting an antibacterial activity.
- LDs interact with phagosomes and appear to be involved in Ag cross-presentation.

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