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Lipid droplets in inflammation and cancer

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ABSTRACT

Accumulation of lipid droplets (also known as lipid bodies or adiposomes) within leukocytes, epithelial cells, hepatocytes and other non-adipocytic cells is a frequently observed phenotype in infectious, neoplastic and other inflammatory conditions. Lipid droplet biogenesis is a regulated cellular process that culminates in the compartmentalization of lipids and of an array of enzymes, protein kinases and other proteins, suggesting that lipid droplets are inducible organelles with roles in cell signaling, regulation of lipid metabolism, membrane trafficking and control of the synthesis and secretion of inflammatory mediators. Enzymes involved in eicosanoid synthesis are localized at lipid droplets and lipid droplets are sites for eicosanoid generation in cells during inflammation and cancer. In this review, we discuss the current evidence related to the biogenesis and function of lipid droplets in cell metabolism and signaling in inflammation and cancer. Moreover, the potential of lipid droplets as markers of disease and targets for novel anti-inflammatory and antineoplastic therapies will be discussed.

1. Introduction

Lipid droplets are lipid-rich cytoplasmic organelles formed by a neutral lipid core surrounded by a monolayer of phospholipids with peculiar composition and exhibiting a diverse array of associated proteins [1,2]. Lipid droplets are the main organelle involved in neutral lipid storage in eukaryotic cells and are constitutively expressed in fat-storing cells, including adipocytes and steroidogenic cells. Although almost absent in most resting non-adipocytic cells, increased numbers of lipid droplets are a described pathologic observation in inflammatory and cancer cells both in experimental settings and in clinical conditions (Fig. 1). Recent studies are starting to shed light on the functions that lipid droplets play in physiological and pathological conditions. Mechanisms that regulate lipid droplet formation and their functional significance to the cell biology of inflammation and tumorigenesis are now under intense scrutiny. Although in the past the presence of lipid droplets in the cells was implicated with storage and lipid trafficking, it is now well established that lipid droplets are highly regulated organelles involved in many aspects of cell activation and metabolism and are involved in the inflammatory and neoplastic processes.

2. Increased lipid droplet biogenesis during inflammation and cancer

2.1. Lipid droplets are ER-derived organelles

It has become increasingly evident that lipid droplet biogenesis involves specific and well-regulated mechanisms, and although the cellular and molecular mechanisms involved are still not completely understood, major advances were made in recent years. The prevailing hypothesis of lipid droplet biogenesis places lipid droplets as endoplasmic reticulum (ER)-derived organelles. Different models of lipid droplet biogenesis have been proposed. The first and still largely accepted model of lipid droplet formation suggests the budding off from the ER into the cytoplasm of the newly formed hydrophobic neutral lipid core surrounded by a monolayer of phospholipids directly derived from the cytoplasmic leaflet of the ER coated with proteins that lack trans-membrane spanning domains [2–5].

Accumulating evidence obtained by different groups has, however, suggested a greater complexity of lipid droplet structure and biogenesis than initially anticipated and new hypothetical models of lipid droplet biogenesis have been proposed [1,4,6–8]. Indeed, different studies reported the presence of membrane-associated and trans-membrane spanning proteins [9–16] as well as ribosomal structures, ribosomal associated proteins and RNA-interacting proteins [6,17,18] within lipid droplets in leukocytes and other cells. In addition, electron microscopy studies have reported images suggestive of membranous structures within

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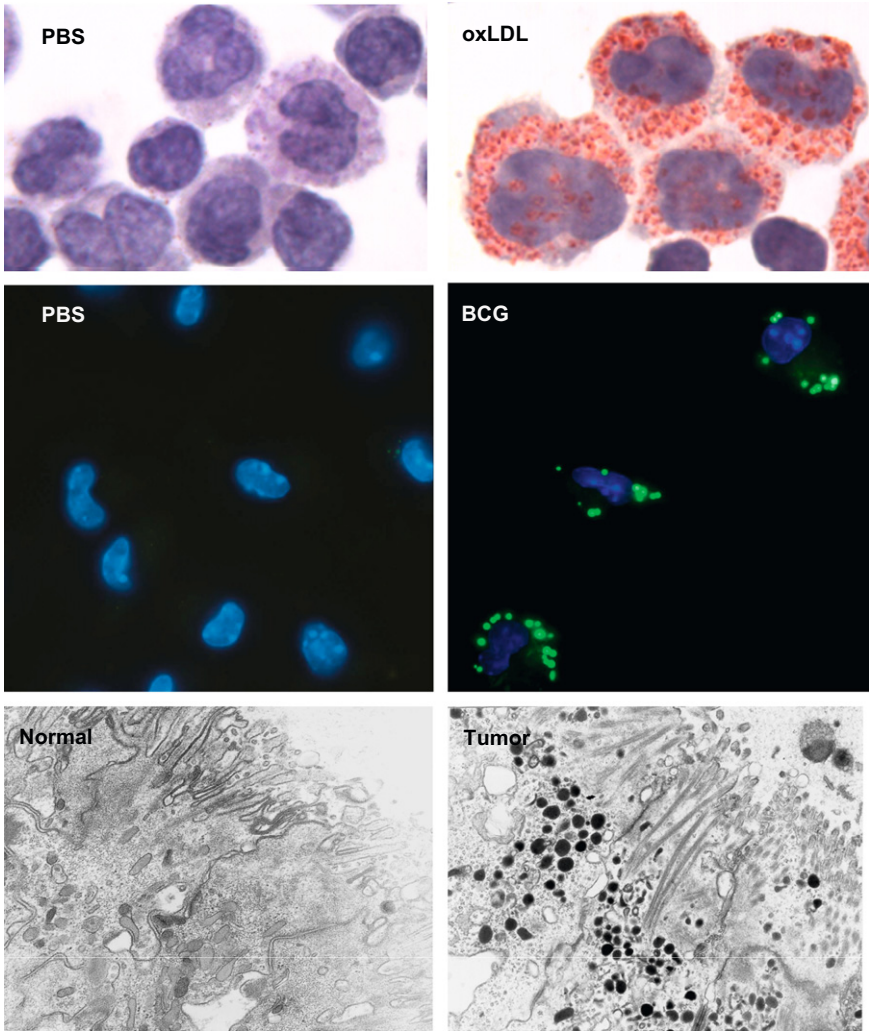

Fig. 1. Increased numbers of cytoplasmic lipid droplets in inflammatory and neoplastic process. Upper panel—lipid droplets in mouse peritoneal cells obtained from 6 h oxLDL-injected mice (OxLDL) as compared with cells from PBS-injected mice (PBS). Lipid droplets in cells were imaged in oil red O stained leukocytes. Middle panel—lipid droplets within mouse macrophages from noninfected (PBS, left panel) or *Mycobacterium bovis*-BCG-infected cells (BCG, right panel) are seen after staining with BODIPY^{TM}493/503 (green). Nuclei are stained with DAPI (blue). Lower panel—analysis of lipid droplets of paired samples of human colon cancer and normal tissue. Pairs of samples of colon cancer and adjacent nonneoplastic tissue obtained at the time of surgery from patients undergoing colon surgical resection as described in [69]. Analysis of thin sections of the adjacent normal tissue (normal, left panel) and colon cancer (tumor, right panel) examined by transmission electron microscopy. Lower panel was reproduced with permission from [69], Copyright 2008 Cancer Research. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

lipid droplets and also the localization of proteins with predicted membrane insertion, including caveolin and cyclooxygenase [9–12,16]. These observations, taken together with findings of in situ enzymatic reactions within lipid droplets such as those involved in eicosanoid production discussed below (Section 3), are suggestive of sub-compartments within the lipid droplet made possible through the incorporation of ER-derived membranes within the forming lipid droplets [1,6].

2.2. *Specific signaling pathways and cell-dependent mechanisms are involved in lipid droplet formation*

Specific and well-regulated signaling pathways have been implicated in lipid droplet biogenesis in leukocytes and other cells involved in inflammatory and/or neoplastic reactions. Among the observations that indicate the existence of regulated production of lipid droplets in inflammatory cells are the findings that saturated fatty acids do not trigger lipid droplet formation while *cis*-unsaturated fatty acids are potent inducers of lipid droplets [19–21], suggestive that lipid droplet formation involves more than simple incorporation of exogenous lipids. Accordingly non-esterifiable *cis*-fatty acids such as the arachidonate analog arachidonyl trifluoromethyl ketone are able to induce formation of new lipid droplets [22]. In addition, lipid droplet formation in macrophages is triggered by oxidized LDL, but not native LDL, indicating the role for receptor-mediated events [23–25]. Moreover, stimulation with cytokines/chemokines and hormones induces receptor-mediated lipid droplet biogenesis not only *in vivo* but even *in vitro* in the absence of exogenous lipids [26–30].

The signaling committed to lipid droplet biogenesis involves different pathways in a stimulus- and receptor-dependent manner. Inflammatory lipid mediators including platelet-activating factor (PAF) and PAF-like molecules [12,19,26,31], but not lyso-PAF, and prostaglandin (PG) D_2 [32] acting via their specific G-protein-linked receptors are potent inducers of lipid droplet formation. Of note, other G-protein-coupled receptor agonists, including interleukin (IL)-8, C5a and leukotriene (LT) B_4, did not induce leukocyte lipid droplet formation, demonstrating the requirement of specific intracellular signaling mechanisms in

the process of lipid droplet biogenesis [19]. Leukocytes incubated with cytokines and chemokines even in the absence of exogenous lipids rapidly form new cytoplasmic lipid droplets by receptor-mediated processes [26,27,30,33,34]. In human eosinophils, IL-5, alone or combined with GM-CSF, as well as immobilized IgG lead to significant increases in lipid droplet numbers [26,34]. CCR3-driven lipid droplet biogenesis was mediated by activation of MAP kinases, PI3K and tyrosine kinases, while PAF effects involved PKC and PLC downstream signaling [19,27].

The formation of lipid droplet-enriched atherosclerotic foam cells involves complex and multi-step mechanisms that depend on different signaling pathways regulating lipid influx, storage and mobilization [23–25]. Different modifications of LDL, including enzymatic modification (E-LDL), acetylation (Ac-LDL), oxidation (Ox-LDL) and glycation (AGE-LDL) followed by recognition and activation of scavenger receptors, mostly CD36, play major roles in lipid accumulation in macrophages [23,25,35–42]. Modified LDL uptake by macrophages through scavenger receptors causes triglyceride and cholesterol loading, followed by cholesterol esterification mediated by acyl coenzyme A:acylcholesterol transferase and storage of cholesteryl esters (CEs) in cytoplasmic lipid droplets [23–25]. Different lipid-derived molecules generated in the process of LDL oxidation are involved in lipid body formation, including PAF-like molecules [31,43], sterol esters [44], oxysterols [45], 1-palmitoyl-2-(5′-oxovaleroyl)-sn-glycero-3-phosphocholine [46] and azelaoyl-phosphatidylcholine [31]. In addition, monocyte chemoattractant protein (MCP-1/CCL2), a key endogenous mediator involved in the pathogenesis of macrophage recruitment and activation in atherosclerosis, is involved in the regulation of macrophage lipid droplet biogenesis in oxidized LDL- and LPS-induced inflammation as well as in experimental sepsis [30,43,47]. MCP-1-driven lipid droplet accumulation is a highly regulated phenomenon, requisitely dependent on the MCP-1 receptor, CCR2 and downstream signaling through MAP- and PI3-kinases [30]. MCP-1-elicited lipid droplet assembly and protein compartmentalization was demonstrated to depend on a functional microtubule network. Accordingly, lipid droplets are enmeshed in a cytoskeleton network in several cell types [6,48–50], and lipid droplet–cytoskeleton interactions were shown also to have roles in lipid droplet motility [51], rapid relocation on cell activation with chemotactic agents [27], lipid droplet fusion and growth [52].

Adipocytokines, including leptin and resistin, were shown to modulate lipid droplet formation in macrophages and may participate in the mechanisms of foam cell formation [28,53,54]. Interestingly, leptin-induced lipid droplet accumulation in macrophages in vivo or *in vitro* is accompanied by increased levels of ADRP [28]. Increased ADRP expression by itself has been shown to be directly related to the enhanced capacity of neutral lipid storage, as ADRP promotes triglyceride and cholesterol storage and reduces cholesterol efflux [55]. ADRP may act also as a nucleation center for the assembly of lipids to form nascent lipid droplets and to enhance droplet stability on lipolytic conditions [56,57]. Recently, an mTOR-dependent pathway was established as an important intracellular player for translational control in the biogenic mechanisms of lipid droplets [54]. Leptin-induced ADRP-enriched lipid droplets were drastically reduced by the treatment with the mTOR inhibitor rapamycin [28]. Indeed, mTOR-dependent translational control of ADRP expression has been suggested in adipocytes stimulated with conjugated linoleic acid and in macrophages stimulated with leptin [28,58].

Transcription-dependent mechanisms are also involved in lipid droplet biogenesis. The best characterized mechanisms involve the activation of SRBP and PPAR transcription factors. PPARγ directly regulates the expression of several genes participating in fatty acid uptake, lipid storage and the inflammatory response, including fatty acid synthase and ADRP [59–61], by binding to specific DNA response elements in target genes as heterodimers with the retinoid X receptors (RXR). Indeed, a role for PPARγ on lipid droplet biogenesis has been established in atherosclerotic and infection triggered reactions [62–66]. Of note, treatment with the fatty acid synthase inhibitor C75 has been shown to significantly inhibit new lipid droplet formation in macrophages induced by apoptotic cells with or without infection [67], in cells infected with dengue virus [68] and in cancerous cells [69], confirming the role of new lipid synthesis in lipid droplet biogenesis.

Upregulated lipogenesis is a common phenotype to numerous human carcinomas and has been associated with poor prognosis in breast, prostate and colon cancer [70,71]. Altered lipid metabolism in cancer cells involves modulation of numerous lipogenic enzymes [70,71], and culminates in the accumulation of newly formed lipids in cytoplasmic lipid droplets. Indeed, enhanced lipid droplet numbers have been described in several neoplastic processes, including adenocarcinoma of the colon (Fig. 1), [69], invasive squamous cervical carcinoma [72], human brain tumor [73] and hepatocarcinoma [11]. To gain further insight on the association of cell transformation and lipid droplet biogenesis, non-transformed intestinal rat epithelial cells (IEC-6 cells) were transfected with a retrovirus construct of a constitutively active H-rasV12. Oncogenic Ras-mediated transformation led to highly increased lipid droplet biogenesis and enhanced PGE_2 production when compared with non-transformed cells [69]. Of note, stimulation of non-transformed intestinal rat epithelial cells with mitogens and activating agents, including treatment with phorbol 12-myristate 13-acetate (PMA) or with unsaturated fatty acids, increased lipid droplet formation [21,69]. Moreover, conditioned media from different human cancer cell lines, including human lung squamous and adenocarcinoma cell lines, acute promyelotic leukemia cell line and human cervical epithelioid carcinoma cell line, but not from non-transformed cells, were able to trigger lipid droplet formation in preadipocytes, thus indicating that cancer cells may also secrete soluble factors that act in a paracrine fashion to induce lipid droplet formation [74].

3. Functions of lipid droplets in inflammation and cancer

3.1. Lipid droplets are sites for eicosanoid formation in inflammation and cancer

It is now becoming increasingly recognized that lipid droplets are specialized locales involved in compartmentalization and amplification of eicosanoid synthesis. Eicosanoids are a family of arachidonic acid-derived signaling lipids that control important cellular processes, including cell activation, migration, proliferation and apoptosis [75,76]. Thus, eicosanoids have key roles in physiological and pathological conditions such as tissue homeostasis, inflammation and cancer [75,76]. Analyses of lipid droplets in different cell types and stimulatory conditions have demonstrated that lipid droplets are particularly active sites for the metabolism of arachidonyl lipids. Electron microscopic, autoradiographic and subcellular fractionation observations demonstrated that arachidonate is incorporated and estherified prominently in lipid droplets of leukocytes, epithelial cells and neoplastic cells [11,77–80]. Free arachidonic acid is an extremely reactive molecule that functions in cell signaling, acting as an intracellular second messenger, as a paracrine mediator of cell activation and as substrate for enzymatic conversion into eicosanoids [75,81]. Although, negligible amounts of free arachidonic acid were identified in lipid droplets, different enzymes involved in arachidonic acid metabolism were demonstrated to localize in lipid droplets, thus providing strong evidence for a

major role for lipid droplets in arachidonic acid metabolism. To have functions in signaling, arachidonic acid present in lipid droplets must be released by phospholipases and the free arachidonate must gain access to eicosanoid-forming enzymes. $cPLA_2$ specifically hydrolyzes arachidonic acid from the sn-2 position of glycerophospholipids and is the rate-limiting enzyme in the formation of eicosanoids and platelet-activating factor [82]. $cPLA_2$ and its activating protein kinases, ERK1 and ERK2, were demonstrated to co-localize at lipid droplets [83]. $cPLA_2\alpha$ localizes to lipid droplets in cells responding to a wide range of stimuli, including arachidonic acid [21,84]. Moreover, high $cPLA_2$ specific activity was present in the lipid droplet fraction [83].

Intracellular compartmentalization of eicosanoid synthesis has emerged as a key feature that regulates the amount and the type of eicosanoid produced. Accordingly, in inflammatory and neoplastic conditions a role for lipid droplets in the enhanced eicosanoid generation was supported by the co-localization of key eicosanoid-forming enzymes. The major enzymes, 5-LO, 15-LO, FLAP and COX, involved in the enzymatic conversion of arachidonic acid into eicosanoids were shown to localize within lipid droplets by different cellular imaging techniques as well as by western blotting from subcellular fractions of lipid droplets stimulated *in vitro* [9,11,12,26,47,69] or obtained from *in vivo* inflammatory responses [28,29,85,86]. Moreover, even the downstream eicosanoid forming enzymes – LTC_4 synthase and PGE_2 synthase – have been demonstrated at lipid droplets [12,14,69]. Collectively, on inflammatory and neoplastic conditions, lipid droplets may compartmentalize the entire enzymatic machinery for eicosanoid synthesis.

Efficient eicosanoid production is not determined only by availability of arachidonic acid and of eicosanoid-forming enzymes, as it requires sequential interactions between specific biosynthetic proteins acting in cascade, and may involve very unique spatial interactions. Therefore, just by detecting eicosanoid-forming enzymes within lipid droplets one cannot establish these organelles as accountable for the efficient and enhanced eicosanoid synthesis observed during inflammatory responses. In support of a role for lipid droplets in eicosanoid formation it has been demonstrated that there are significant correlations between lipid droplet formation and enhanced generation of both LO- and COX-derived eicosanoids *in vitro* [12,19,26,30,34,87,88] as well as *in vivo* [28,29,31,85,86,89], suggesting that increased lipid droplet numbers in cells would result in enhanced capacity of eicosanoid production. The demonstration that lipid droplets can properly arrange enzymatic complexes with successful eicosanoid-forming properties and, therefore, function as specialized domains for focal eicosanoid generation was obtained by the direct intracellular localizations of newly formed eicosanoids. Direct assessment of specific intracellular sites of eicosanoid synthesis has been elusive, as those lipid mediators are newly formed, not stored and often rapidly released on cell stimulation. By means of a newly developed technique – eicosacell – which uses a strategy to covalently cross-link, capture and localize newly formed eicosanoids at their sites of synthesis (reviewed in [90]), it was established that lipid droplets are major intracellular locales for the activation-elicited formation of LTC_4 in eosinophils [27,29,91], LTB_4 in neutrophils and macrophages [30] and PGE_2 in macrophages and epithelial cells [21,69,80,86].

Importantly, eicosanoid formation within lipid droplets is not restricted to leukocytes or to inflammatory conditions. Cells that produce high quantities of eicosanoids under physiological conditions, including granulosa cells of periovulatory follicles involved in the production of PGE_2, which is necessary for normal ovulation [92], luteal steroid-producing and interstitial cells involved in regression of the corpus luteum [13], and fetal membranes with advancing gestation and labor [14,93], were demonstrated to exhibit high numbers of lipid droplets containing eicosanoid synthesizing enzymes. Moreover, endothelial and epithelial cells involved in pathological conditions such as in cancer, hypoxia and during infections were shown to contain increased numbers of eicosanoid-synthesizing lipid droplets [9–11,69,80,94].

3.2. Lipid droplets in cell metabolism and proliferation

Although recently published data suggest that the increase of lipid droplet numbers occurring in cells undergoing cell proliferation is a common feature in many neoplastic processes and may contribute towards cell proliferation, no definitive studies are presently available that establish a causal link between the increase of the lipid droplet numbers and the development of cancer.

Of relevance to the roles of lipid droplets in cell metabolism and proliferation, a variety of signaling-associated proteins have been demonstrated to compartmentalize within lipid droplets, suggesting a key role for this organelle as a cytoplasmic domain with roles in intracellular signaling. Indeed, proteins with well-established roles in the pathogenesis of inflammation and of oncogenic cell transformation, tumorigenesis and metastasis including PI3K, ERK1, ERK2, p38, PKC and caveolin were shown to localize in lipid droplets in a variety of cell types [83,95–99]. The MAP kinases ERK1, ERK2 and p38 are key enzymes in the activation of $cPLA_2$, the enzyme that specifically hydrolyzes arachidonic acid from the *sn*-2 position of glycerophospholipids. The association of $cPLA_2$ activators ERK1 and ERK2 with lipid droplets may contribute to efficient phosphorylation of $cPLA_2$ on lipid droplets in response to extracellular stimuli. PI3K regulatory and catalytic subunits were also localized to lipid droplets in a human histiocytic lymphoma cell line and in PAF-stimulated human neutrophils [95]. Of note, co-immunoprecipitation studies demonstrated PI3K to be physically associated with phosphorylated Lyn kinase in induced lipid droplets of human neutrophils [95]. Although functional studies still need to be carried out to characterize the actual roles of lipid droplet-resident kinases, accumulating evidence indicates that kinase-mediated signaling is active within cytoplasmic lipid droplets in leukocytes.

Potential functions of lipid droplets as sites of ribosomal translation and de novo protein synthesis have been proposed with potential implications for the regulation of cancerous- and inflammation-related processes. EM analyses of lipid droplets have demonstrated the presence of ribosomes or particles resembling ribosomal subunits [6,17,18]. Moreover, ribosomes or ribosome subunit-like particles were present within the lipid-rich cores and/or attached to lipid droplets surface in human histiocytic lymphoma cell line U937 and in activated human neutrophils and eosinophils [6]. That lipid droplets may be sites of ribosomal function is supported by the demonstration in lipid droplets of ^{3}H-uridine accumulation and mRNA detection by *in situ* hybridization [17,18]. Moreover, proteomic analyses of purified leukocyte-derived lipid droplet fractions identified several ribosomal subunit proteins as well as translation initiation factors [6]. Accordingly, proteomic analyses of lipid droplets from a hepatoma cell line expressing the capsid protein from hepatitis C virus have also identified ribosomal and RNA-interacting proteins [100]. Future investigations are necessary to characterize the roles of lipid droplets in the regulation of local protein synthesis during inflammation and cell transformation.

A positive correlation of lipid droplets and cell proliferation has been recently established in colon cancer cells [69], suggesting an involvement of lipid droplets in cell proliferation and with potential implications to the pathogenesis of colon adenocarci-

noma. Accordingly, an association of lipid droplets has also been observed in the regenerating liver [101]. The first mechanistic insights on how lipid droplets may participate in cell proliferation were provided by studies in yeast, suggestive of a direct link between cell cycle-regulatory kinases and lipid droplet-derived triglyceride degradation by the demonstration of a role for cyclin-dependent phosphorylation of tgl4 with mobilization of lipid droplets, which participate in the coordinated membrane synthesis with cell-cycle progression [102].

4. Potential for lipid droplets as disease markers and therapeutic targets

The observation that neoplastic cells and tissues exhibited highly increased numbers of lipid droplets and increased expression of the lipid droplet-specific protein ADRP has highlighted the possibility of using the detection of lipid droplets and/or ADRP as biomarkers in cancer. Accordingly, ADRP quantification has been recently proposed as a potential diagnostic and prognostic biomarker for renal cell and hepatocellular carcinoma [103,104].

As discussed above, lipid droplets may function as specialized intracellular sites of signaling within cells engaged in inflammatory process ranging from infections to atherosclerosis and cancer. Although no specific lipid droplet inhibitor has been described so far, different classes of drugs as well as gene knockdown of PAT (perilipin, ADRP and TIP 47) proteins have been demonstrated to inhibit lipid droplet formation. The hypothesis of lipid droplet inhibition as target for anti-inflammatory therapy has been tested in different model systems.

Inducible mechanisms that regulate eicosanoid production are attractive targets for pharmacological intervention. Aspirin and selected other non-steroidal anti-inflammatory drugs (NSAIDs) inhibited lipid droplet formation *in vivo* and *in vitro* [29,87,105]. However, the mechanisms involved in NSAID inhibition of lipid droplet biogenesis are not completely understood. Interestingly, it has been demonstrated that COX-independent mechanisms are involved in lipid droplet inhibition—*cis*-unsaturated fatty acids induced formation of new lipid droplets even in macrophages from COX-1- and COX-2-deficient mice, and NSAIDs, including aspirin, sodium salicylate, indomethacin and NS-398, inhibited lipid droplet formation equally in macrophages from wild-type and COX-1- or COX-2-deficient mice [87,105].

Approaches to inhibit lipid accumulation in macrophage foam cells may be of therapeutic value in preventing atherosclerosis and have been recently reviewed elsewhere [24]. Different strategies to inhibit lipid droplet formation have been tested to address the role of macrophage lipid droplets as targets for therapeutic intervention in atherosclerosis. ADRP expression facilitates foam cell formation induced by modified lipoproteins in mouse macrophages *in vitro*; conversely ADRP gene inactivation in apolipoprotein E-deficient mice reduces the number of lipid droplets in foam cells in atherosclerotic lesions and protects the mice against atherosclerosis [106]. ACAT inhibitors, including the fungal-derived cyclodepsipeptides, showed potent inhibitory activity of lipid droplet accumulation in mouse peritoneal macrophages and exerted anti-atherogenic activity in both low-density lipoprotein receptor and apolipoprotein E-knockout mice [107].

A role for lipid droplet inhibition in host response to infection has been proposed [108]. Accumulating evidence supports the hypothesis that lipid droplet-derived endogenous PGE_2 down-modulates the macrophage response by inhibiting mycobacteria-induced TNF production and increasing the levels of the anti-inflammatory cytokine IL-10, and as such, pharmacological inhibition of either prostaglandin production or lipid droplet formation would have beneficial effects to the host to control the infection [67,86]. Accordingly, PPARγ inhibition in macrophages not only leads to decreased lipid droplet biogenesis but also enhances macrophage mycobacterial killing, supporting the hypothesis that lipid droplets may have implications in the pathogenesis of mycobacterial infection [66]. Inhibition of lipid droplet formation or the disruption of capsid viral protein association with lipid droplets leads to decreased viral particle formation in dengue [68] and hepatitis C infection [109,110], suggesting an effect of lipid droplets in viral replication.

Clinical and experimental evidence strongly suggests that NSAIDs are anticarcinogenic, antiproliferative and antineoplastic. In fact, the oncogenic potentials of the prostaglandins are related to their abilities to promote cell proliferation and inhibit apoptosis in intestinal epithelial cells [111–113]. However, it is still not clear whether the antineoplastic effect of aspirin could be attributable exclusively to its ability to inhibit prostaglandin production. A role for lipid droplets as a potential target to generate new drugs for cancer treatment has been recently suggested [69]. The human colon cancer cell line CACO-2 presents a progressive growth when compared with non-transformed epithelial intestinal cells. Colonic adenocarcinoma cells contain increased numbers of lipid droplets with documented PGE_2 synthase localization and focal PGE_2 synthesis. Inhibition of lipid droplet formation by aspirin correlated with both inhibition of PGE_2 generation and cell proliferation in CACO-2 and IEC-6H-rasV12 transformed cells [69]. A similar effect was obtained with lipid droplet inhibition by C75, a fatty acid synthase inhibitor. Interestingly, although C75 is not a COX inhibitor, it significantly inhibited PGE_2 production and the proliferation of colon cancer cells [69]. The inhibition of lipid body generation may affect the subcellular compartmentalization of COX-2 and in consequence inhibit the enhanced prostaglandin synthesis that is related to the pathogenesis of colon cancer.

5. Concluding remarks

Lipid droplets may influence cell functions through a variety of complex mechanisms and these mechanisms are now beginning to be unraveled. Our contemporary view of lipid droplets places this organelle as a key regulator of different inflammatory and neoplastic diseases and potential biomarkers of cell activation and disease. Lipid droplet biogenesis is highly regulated and is cell and stimulus specific. Studies of lipid droplet structural features have revealed a much more complex structure than initially anticipated—besides lipids, lipid droplets include a diverse array of proteins that may vary according to the cell type and cellular activation state and thus may determine different functions for these organelles. The further identification of key pathways, molecules and functions of lipid droplets may enable the development of therapeutic targets for future intervention in diseases that progress with increased lipid droplet accumulation as in atherosclerosis, hepatic steatosis, cancer and inflammation. Of note, future studies targeted to the development of selective lipid droplet inhibitors will be of great interest. Moreover, investigations will be necessary to characterize the safety of lipid droplet inhibition since lipid accumulation within lipid droplets may participate in protective mechanisms of lipid homeostasis against cellular lipotoxicity.

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