



Lipid-laden macrophages in atherosclerosis and cancer

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ABSTRACT

This review explores the dual roles of lipid-laden macrophages (LL-Macs) in inflammation, atherosclerosis and cancer, emphasizing both their shared and divergent functions across physiological and pathological conditions. Lipid metabolism regulates the polarization of macrophages in homeostasis and inflammation. In atherosclerosis, LL-Macs contribute to plaque formation and inflammation, while in cancer, LL-Macs play crucial roles in immune suppression and tumor progression. The article outlines the molecular mechanisms driving macrophage lipid accumulation in each of these scenarios and how the process is influenced by the distinct local microenvironments in inflammation, atherosclerosis and cancer. Single-cell RNA sequencing (scRNA-seq) studies have identified both common and unique gene signatures between LL-Macs in atherosclerosis and cancer, reflecting the varying microenvironmental cues that shape macrophage function and disease outcomes. Finally, we examine lipid-modulating strategies in atherosclerosis, assess their potential in cancer treatment, and highlight research gaps for developing new LL-Macs targeted therapies in cancer.

Abbreviations: ABC, ATP-binding cassette; ACC2, Acetyl-CoA carboxylase 2; ACAT1, Acetyl-Coenzyme A Acetyltransferase 1; ACLY, ATP-citrate lyase; ATGL, adipose triglyceride lipase; BCAAs, branched-chain amino acids; CD, 2-Hydroxypropyl-β-cyclodextrin; CPT1A, carnitine palmitoyltransferase 1; CPT2, carnitine palmitoyltransferase 2; CES1, carboxylesterase 1; CVD, cardiovascular disease; DG, diacylglycerol; DGAT1, diacylglycerol acyltransferase 1; DHCR24, 3β-hydroxysterol Δ24-reductase; ER, endoplasmic reticulum; ETC, electron transport chain; FA, fatty acid; FAO, fatty acid oxidation; FADH2, flavin adenine dinucleotide; FAS, fatty acid synthesis; FC-Macs, Foam cell macrophages; GLUT, glucose transporter; HIF-1α, Hypoxia-inducible factor 1-alpha; HSL, hormone-sensitive lipase; HDL, high-density lipoprotein; INSIG1, Insulin induced gene-1; LDL, low-density lipoproteins; LDAH, LD-associated hydrolase; LIPA, Lysosomal acid lipase; LL-Macs, lipid-laden macrophages; LL-TAMs, lipid-laden tumor-associated macrophages; LPS, lipopolysaccharide; LOX-1, lectin-like oxidized LDL receptor-1; LRP-1, low-density lipoprotein receptor-related protein 1; LXR, liver X receptors; MAGL, monoacylglycerol lipase; MCAD, medium-chain acyl-CoA dehydrogenase; MUFAs, mono-unsaturated fatty acids; NADH, nicotinamide adenine dinucleotide; NCEH1, neutral cholesterol ester hydrolase 1; nHDL, nascent high-density lipoprotein; NO, nitric oxide; oxLDL, oxidized low-density lipoproteins; OXPHOS, oxidative phosphorylation; PPAR, peroxisome proliferator-activated receptor; PPP, pentose phosphate pathway; PUFAs, polyunsaturated fatty acids; ROS, reactive oxygen species; scRNA-seq, single-cell RNA sequencing; SR-BI, scavenger receptor class B type I; SDH, succinate dehydrogenase; SCD2, stearoyl-CoA desaturase 2; SREBP, Sterol regulatory element-binding protein; TAM, tumor-associated macrophage; TCA cycle, tricarboxylic acid cycle; TG, triglyceride; TME, Tumor microenvironment; VLDL, very low-density lipoprotein; VSMCs, vascular smooth muscle cells.

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1. Introduction

Macrophages play pivotal roles in tissue homeostasis, orchestrating innate immune responses, activating adaptive immunity, and contributing to the pathogenesis and progression of various diseases, including CVD and cancer [1–7]. As highly plastic immune cells, macrophages adapt to their microenvironment, acquiring distinct polarization states—spanning a spectrum from the pro-inflammatory M1-like phenotype to the anti-inflammatory M2-like phenotype—that dictate their functional outcomes [8]. In recent years, the accumulation of lipids within macrophages, referred as lipid-laden macrophages (LL-Mac), has emerged as a critical factor in the pathogenesis, progression, and therapeutic response of both atherosclerosis, a major component of CVD, and cancer [9,10]. This dual involvement underscores the complex interplay between lipid metabolism, macrophage function, and disease progression, positioning LL-Mac as a focal point for understanding and potentially intervening in both pathological conditions.

Atherosclerosis, characterized by the buildup of lipid-rich plaques in arterial walls, represents a leading cause of cardiovascular morbidity and mortality worldwide [11]. Within atherosclerotic lesions, macrophages engulf oxidized low-density lipoproteins (oxLDL) and other lipid species, leading to lipid accumulation and the formation of lipid-laden macrophages (LL-Macs), commonly referred to as foam cell macrophages (FC-Macs) [12,13]. This term distinguishes FC-Macs from other lipid-accumulating foam cells in the plaque, such as vascular smooth muscle cells (VSMCs). FC-Macs contribute to chronic inflammation, plaque instability, and eventual rupture, increasing the risk of myocardial infarction and stroke [14]. Lipid overload alters FC-Mac function and shifts their polarization toward pro-inflammatory M1-like states, exacerbating inflammation [15]. However, the balance between M1-like and M2-like phenotypes within atherosclerotic plaques remains dynamic [3]. scRNA-seq and other high-throughput analyses of atherosclerotic plaques in human patients and mouse models, have revealed many of the transcriptomic and epigenetic mechanisms involved in foam cell formation [16,17]. This new understanding is crucial for unraveling the mechanisms of atherosclerosis and identifying novel therapeutic targets to stabilize plaques and reduce cardiovascular risk.

Similarly, in cancer, tumor-associated macrophages (TAMs) are integral to the tumor microenvironment (TME) [18]. The polarization of TAMs toward an anti-inflammatory M2-like phenotype promotes tumor growth, metastasis, therapy resistance, and immune evasion. While the role of FC-Macs has long been established in atherosclerosis, the significance of lipid-laden TAMs (LL-TAMs) in cancer has only recently garnered attention [7,19]. Loading of lipids derived from cancer cells drives the polarization of TAMs toward a pro-tumorigenic (anti-phagocytic, proangiogenic) state and activates proliferative and pro-survival signaling pathways (e.g., XBP1, STAT3, PI3K, mTORC2) in cancer cells [20,21]. The metabolic reprogramming of LL-TAMs not only supports cancer progression but also contributes to immunosuppression, creating a permissive environment for tumor survival and spread [7,20,22,23]. Consequently, a higher abundance of LL-TAMs in the tumor microenvironment correlates with poor prognosis and reduced response to treatment in cancer patients—including those with glioblastoma, breast, colon, ovarian, prostate, and hepatocellular carcinomas, as well as colorectal liver metastasis—highlighting their pathogenic role and potential as prognostic and predictive biomarkers and therapeutic targets [9,20,21,24–26].

Despite the common presence of LL-Macs in both atherosclerosis and cancer, the specific mechanisms governing lipid loading and their roles differ due to distinct microenvironmental cues and disease contexts. In atherosclerosis, lipid accumulation primarily results from systemic lipid dysregulation, such as elevated low-density lipoprotein (LDL) levels, and local oxidative stress, leading to FC-Mac formation and plaque development [11,12]. In contrast, lipid loading in LL-TAMs involves tumor-derived lipids and paracrine signaling within the TME, driving TAM polarization and tumor-supportive functions [7]. Nevertheless,

LL-Macs in both conditions share a common pathogenic effect: lipid metabolism influences macrophage polarization and function, bridging inflammation, immune regulation, and disease progression. This overlap suggests that insights from one disease may enhance our fundamental understanding of pathogenesis and inform strategies for the other, potentially revealing shared pathways or therapeutic opportunities.

This review examines the multifaceted roles and mechanisms of LL-Macs in homeostasis, atherosclerosis, and cancer, with a particular emphasis on how lipid metabolism shapes macrophage phenotype and function. By integrating these perspectives, we highlighted LL-Macs as a shared cellular component in both diseases and explored their underlying mechanisms and therapeutic potential. Earlier reviews have addressed the role of lipid metabolism in cancer cells [27–29] and in macrophages [30,31] as drivers of tumor progression and resistance to therapy. Others have explored the epidemiological links between cardiovascular disease (CVD), metabolic disorders, and cancer, emphasizing shared mechanisms and risk factors [32–34]. This review aims to contribute to the extant literature by offering an updated synthesis and discussion of common and distinct lipid signaling pathways in LL-Macs in atherosclerosis and cancer. It also compares their transcriptomic signatures using integrated scRNA-seq data across both disease contexts.

The rest of the article is organized as follows: First, we examine lipid metabolism in macrophages during polarization between M1-like and M2-like states, exploring how lipid catabolism, synthesis, uptake, storage, and efflux regulate this spectrum of phenotypic and functional outcomes. Second, we investigate the role of FC-Macs in atherosclerosis, detailing their contribution to plaque formation, inflammation, and cardiovascular risk. Third, we summarize the literature on LL-TAMs in cancer, focusing on their impact on tumor progression and immune evasion. Fourth, leveraging scRNA-seq data from atherosclerosis and pan-cancer in human patients, we identify common molecular signatures between LL-Macs in both pathologies. Fifth, we summarize current knowledge on drugs targeting lipid metabolic dysregulation in atherosclerosis, as well as their application in targeting cancer in mouse models, clinical trials, or clinical practice.

2. Immunometabolism as a driver of macrophage phenotype and function

Macrophages are extraordinarily plastic cells, performing a spectrum of functions vital to homeostasis and immune defense. Their ability to transition from immune sentinels to inflammatory effectors that combat infections, and ultimately to reparative phenotypes that resolve tissue damage, highlights their functional plasticity [1,35]. Central to this adaptability is their dynamic metabolism, which serves as both a regulator and an effector of cellular function. Over the past decade, macrophage immunometabolism has emerged as a prominent field of study, unveiling the intricate relationship between metabolic pathways and macrophage behavior—an interplay that is particularly critical in the formation and function of LL-Mac in diseases like atherosclerosis and cancer, as discussed in the introduction.

Lipid metabolism plays a critical role in maintaining macrophage homeostasis, and its dysregulation contributes to pathogenesis in various pathological contexts. Macrophage metabolism integrates multiple pathways, including glycolysis, the tricarboxylic acid (TCA) cycle, oxidative phosphorylation (OXPHOS), the pentose phosphate pathway (PPP), amino acid metabolism, fatty acid oxidation (FAO), and fatty acid synthesis (FAS) [36]. Although these pathways are frequently associated with macrophage phenotypes—pro-inflammatory (M1-like) or anti-inflammatory (M2-like)—this dichotomy represents an oversimplification, largely derived from *in vitro* studies. Such experimental conditions often fail to replicate the intricate and dynamic nature of inflammation *in vivo* [37]. In reality, macrophage metabolism within an *in vivo* system—such as in atherosclerotic plaques or the TME—is shaped by temporal and spatial factors and influenced by continuous crosstalk with other cell types [8,38]. This complexity challenges attempts to

define macrophage metabolic states using linear or overly simplistic models.

Under homeostatic conditions, macrophages rely predominantly on OXPHOS for energy production. Pyruvate enters the TCA cycle, where it is converted into acetyl-CoA, serving as a central hub for generating citrate that supports cholesterol and FAS [39] (Fig. 1). The TCA cycle also produces reducing equivalents—nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide (FADH₂)—which donate electrons to the electron transport chain (ETC) to drive OXPHOS and ATP production [40]. In inflammatory states, macrophages typically shift their metabolism toward glycolysis [41]. However, evidence suggests that OXPHOS may remain active or even become upregulated

under certain inflammatory conditions [39,42]. This variability likely reflects differences in macrophage origin, timing, and environmental context, highlighting the need for a refined understanding of metabolic regulation during inflammation.

Upon detecting inflammatory signals, macrophages activate glycolysis to rapidly meet energy demands and produce intermediates essential for immune functions. Glucose is transported into the cytosol via glucose transporters (GLUTs) and converted into pyruvate, yielding two ATP molecules per glucose molecule [43,44]. Pyruvate generated during glycolysis can feed into lactate production, which supports reparative macrophage functions [45]. Inflammatory signals also disrupt the TCA cycle, leading to the accumulation of citrate and succinate [46]. Citrate

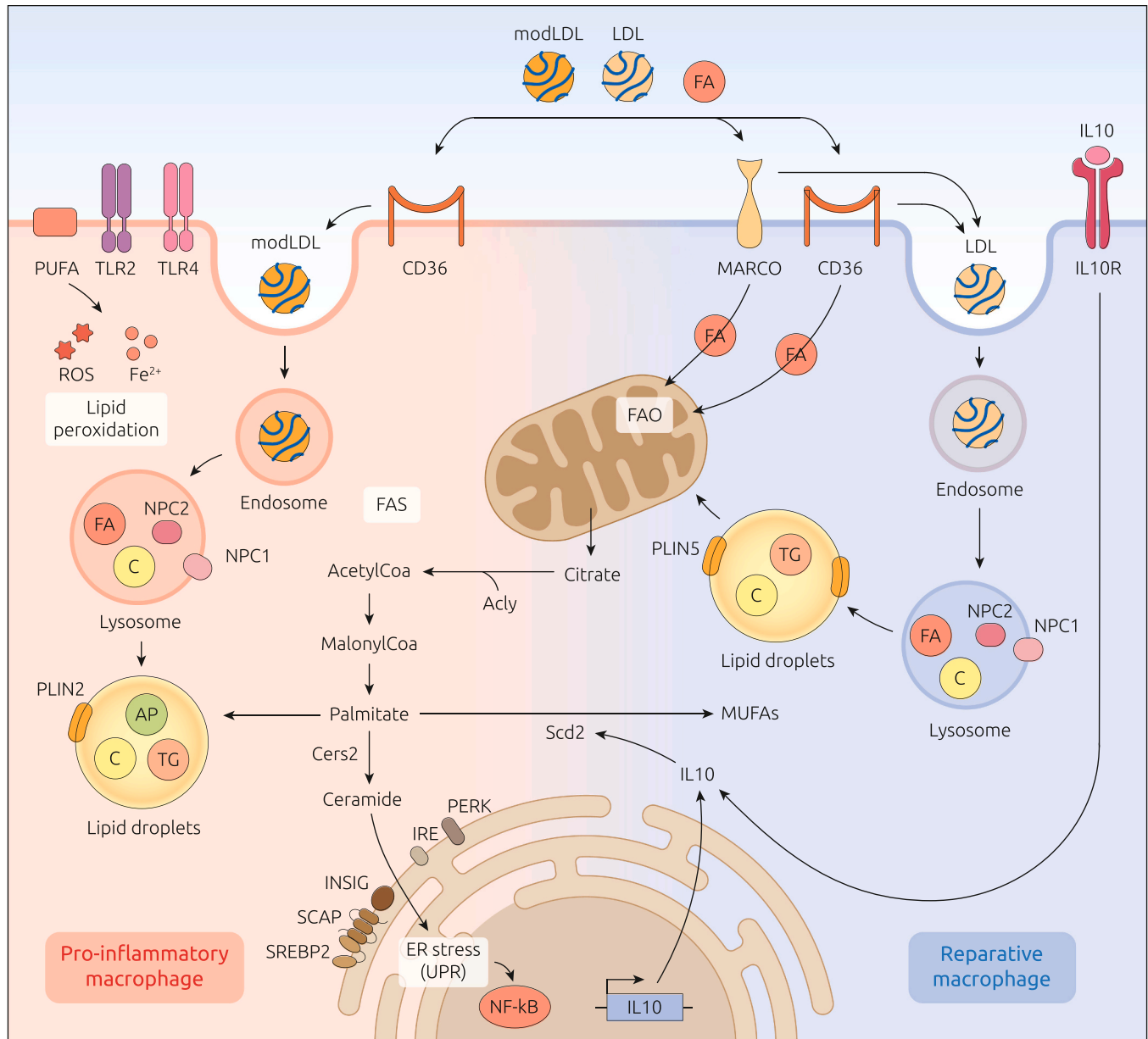


Fig. 1. Lipid metabolism in M1-like (pro-inflammatory) and M2-like (reparative) macrophages. Under inflammatory conditions, macrophages increase lipid uptake and process these lipids in lysosomes. Neutral lipids are stored in LD, which contain antimicrobial peptides, TG, and cholesterol. LDs express PLIN2 that limits LD-mitochondria contact, thereby restricting FAO. Additionally, lipids can be synthesized de novo via FAS, using citrate exported from mitochondria. These newly formed lipids may be stored in LDs or converted into bioactive lipids, such as ceramides, which contribute to inflammation and can trigger the UPR and in turns NF-κB activation. Excess of ROS and accumulation of PUFAs can lead to lipid peroxidation, exacerbating inflammatory responses and promoting cell damage. In contrast, reparative macrophages primarily use lipids as an energy source through mitochondrial FAO. LDs express PLIN5, which facilitates LD-mitochondria interactions and supports efficient lipid catabolism. Furthermore, IL-10 signaling enhances lipid metabolism through SCD2, reducing the accumulation of pro-inflammatory sphingolipids and ceramides, thereby contributing to the resolution of inflammation. See main text for further details.

supports FAS for phospholipid biogenesis and the production of inflammatory lipid mediators, such as prostaglandins [47]. Succinate stabilizes hypoxia-inducible factor 1- α (HIF-1 α), even in normoxic conditions, promoting the expression of glycolytic and pro-inflammatory genes. Additionally, succinate oxidation via succinate dehydrogenase (SDH) induces reverse electron transport at complex I in mitochondria, contributing to reactive oxygen species (ROS) production [48]. This mitochondrial ROS is critical for pathogen clearance and further stabilizes HIF-1 α , amplifying inflammatory macrophage activity. The PPP serves as an oxidative alternative to glycolysis, where glucose oxidation reduces NADP⁺ to NADPH, which is involved in ROS production [49]. Under inflammatory conditions, macrophages also use NADPH from the PPP to generate antioxidants that mitigate oxidative damage, as well as to support cholesterol synthesis [50] and produce ribose-5-phosphate for nucleotide and nucleic acid synthesis [51].

Amino acid metabolism also plays a pivotal role in macrophage activity, often reflecting the balance between pro- and anti-inflammatory states. Arginine metabolism exemplifies this duality: it can be converted to nitric oxide (NO) in pro-inflammatory macrophages or to polyamines in anti-inflammatory states [52]. Similarly, glutamine and tryptophan are metabolized differently depending on macrophage polarization [53, 54], with branched-chain amino acids (BCAAs) typically associated with pro-inflammatory functions [42]. Furthermore, macrophages can deplete certain amino acids, such as tryptophan or arginine, to suppress intracellular pathogens [55,56], highlighting their metabolic adaptability in immune defense.

Lipid metabolism enables macrophages to adapt to their environment and modulate immune responses. It contributes not only to energy homeostasis but also to the regulation of signaling pathways that influence macrophage phenotype and function, ultimately driving the formation of FC-Macs in atherosclerosis and LL-TAMs in cancer. FAO is the primary pathway for degrading fatty acids (FA) and is often associated with anti-inflammatory macrophages, which require high energy levels to facilitate tissue repair and inflammation resolution [57–59]. While energetically efficient, producing over 100 ATP molecules per fatty acid [60], FAO is not strictly essential for M2-like polarization. For instance, pharmacological inhibition of FAO using etomoxir or carnitine palmitoyltransferase II (CPT2) blockade does not entirely abrogate anti-inflammatory macrophage polarization under IL-4 stimulation [61, 62]. Interestingly, FAO can also activate the inflammasome [63] and contribute to pro-inflammatory and anti-tumorigenic responses [54], underscoring its dual role in macrophage biology. In fatty acid biogenesis, cytosolic citrate is converted by ATP-citrate lyase (ACLY) into acetyl-CoA, the building block for FAS [64]. In contrast to FAO, FAS is predominantly associated with pro-inflammatory macrophages [41,65] (Fig. 1). Stimuli such as lipopolysaccharide (LPS) increase FAS activity by driving glycolysis and the PPP, generating acetyl-CoA and NADPH for lipid biosynthesis. Newly synthesized fatty acids serve as precursors for inflammatory lipid mediators and support membrane remodeling during phagocytosis, enhancing macrophage antimicrobial activity [66,67]. Sterol regulatory element-binding proteins (SREBPs) are key regulators of this process and are also implicated in inflammasome activation [68] and inflammation resolution [69], further linking lipid metabolism to inflammatory signaling.

Macrophages process environmental lipids through various mechanisms, including the uptake of lipoproteins—such as modified LDLs and very low-density lipoproteins (VLDLs)—via scavenger receptors, as well as through efferocytosis, macropinocytosis, and phagocytosis [70]. However, excessive cholesterol accumulation can lead to the formation of FC-Macs. For instance, uptake of oxLDL through CD36 triggers lipid accumulation, inflammation, and apoptosis in macrophages due to an overall excess of cholesterol [71]. In a hyperlipidemic environment, monocytes and macrophages lose HLA-DR molecules, which are

associated with an immunocompetent phenotype [72,73]. Once acquired, lipids can be processed in lysosomes into free fatty acids (FAs) and cholesterol [74]. Additionally, lipids can be synthesized *de novo* through FAS. In both cases, excessive lipid accumulation poses significant risks to macrophage health, including toxicity and dysfunction [75], which contribute to the pathogenic roles of FC-Macs in atherosclerosis and LL-TAMs in cancer.

To prevent toxicity, macrophages esterify free cholesterol in the endoplasmic reticulum (ER) and store lipids in cytosolic lipid droplets (LDs). LDs are specialized organelles with a core of neutral lipids surrounded by a phospholipid monolayer, assembled in the ER [76]. These structures function as protective hubs, sequestering excess lipids and preventing harmful processes like lipid peroxidation and ferroptosis. LD assembly involves diacylglycerol O-Acyltransferase-1 (DGAT1)-mediated triglyceride (TG) synthesis, and their abundance is linked to macrophage phenotype and inflammatory status. DGAT1 inhibition is associated with decreased pro-inflammatory responses [77], and the deficiency in the lipolytic enzyme adipose triglyceride lipase (ATGL) reduces inflammation and phagocytic capacity, favoring an anti-inflammatory state [78,79].

In conditions of lipid overload, macrophages rely on lipid efflux pathways to prevent harmful cholesterol accumulation. This involves exporting lipids via ATP-binding cassette (ABC) transporters like ABCA1 and ABCG1, which transfer lipids to high-density lipoproteins (HDLs) [80]. Alternatively, macrophages may process stored lipids through lipolysis, breaking down triglycerides inside LDs into free FAs and glycerol. This process requires lysosomal acid lipases and leads to the production of acyl-CoA, which can enter mitochondria for β -oxidation through the FAO pathway [81]. FAO generates acetyl-CoA, NADH, and FADH₂, which feed into the TCA cycle and OXPHOS for ATP production.

Interestingly, TCA cycle-produced itaconate stabilizes the expression of carnitine palmitoyltransferase 1 (CPT1A), a key enzyme in FAO, protecting against lipid peroxidation and ferroptosis [82]. This highlights the interconnected roles of LDs, the TCA cycle, and FAO in maintaining lipid homeostasis and macrophage survival under metabolic stress, a balance that is disrupted in the formation of FC-Macs and LL-TAMs.

Beyond lipid storage and degradation, macrophages actively synthesize new lipids through FAS, using precursors from other metabolic pathways to generate FAs that support inflammatory responses. These newly synthesized FAs serve as precursors for inflammatory mediators, such as prostaglandins like prostaglandin E₂ (PGE₂), and facilitate membrane remodeling, which is critical for phagocytosis and pathogen elimination [83]. SREBPs play a central role in regulating this lipid synthesis and are also implicated in inflammasome activation [9].

Inflammatory signals often stimulate LD formation in macrophages. LDs are not merely passive storage sites; they actively regulate inflammatory responses by storing mediators such as leukotrienes and prostaglandins (e.g., PGE₂), which modulate inflammation [83,84] (Fig. 1). LDs also interact with mitochondria and the ER, facilitating lipid transfer and inter-organelle communication [85]. Furthermore, they harbor antimicrobial molecules capable of pathogen elimination, underscoring their immunological significance. In this context, LD localization is essential. In inflammatory conditions, PLIN5 is down-regulated in LDs, reducing their contact with mitochondria and oxidative metabolism, whereas PLIN2 is upregulated [86]. By storing polyunsaturated fatty acids (PUFAs), LDs protect macrophages from lipid peroxidation and ferroptosis, processes exacerbated by ROS and redox-active iron [87].

LDs are integral to the pro-inflammatory response but also participate in inflammation resolution. They act as reservoirs for molecules like PGE₂, which can function as both pro- and anti-inflammatory mediators depending on the context [83,84]. This dual role suggests temporal

regulation, with LDs contributing to the initiation of inflammation and later to its resolution. This adaptive function highlights why macrophages enhance lipid synthesis during the onset of inflammation—not only to fuel the pro-inflammatory response but also to prepare for subsequent resolution.

Recent evidence reinforces this notion, demonstrating that lipids serve as central regulators of inflammation resolution. York et al. showed that this process is mediated by IL-10 and stearoyl-CoA desaturase 2 (SCD2), with monounsaturated fatty acids (MUFAs) limiting inflammation by reducing sphingolipid and ceramide levels [88]. These findings emphasize the dynamic and multifaceted role of lipid metabolism in both the inflammatory response and its resolution.

Elevated levels of cholesterol or saturated FAs in macrophages trigger ER stress—through ER stress receptors IRE1 α , PERK, and ATF6—and the unfolded protein response (UPR) (Fig. 1). When lipid overload becomes excessive, the resulting ER stress induces the release of pro-inflammatory mediators or leads to cell death [89,90]. These processes are implicated in the progression of chronic inflammatory diseases like atherosclerosis and cancer, exacerbating their severity by promoting the pathogenic functions of FC-Macs and LL-TAMs.

Understanding the dynamics of lipid synthesis and oxidation in inflammatory macrophages provides valuable insights into pathological processes. FC-Macs are characterized by cholesteryl ester-rich LDs that originate primarily from the uptake of LDL particles in the atherosclerotic microenvironment [91]. In contrast, LL-TAMs in the TME play a pivotal role in tumor progression, interacting with tumor cells and other TME components. Unlike FC-Mac in atherosclerotic lesions, which primarily accumulate cholesteryl esters, the lipid profile of LL-TAMs is dominated by triglycerides, glycerophospholipids and sphingomyelins [20]. The source of these lipids remains unclear; they may be derived from tumor cells, other TME cells, or alternative endogenous pathways. Evidence indicates that lipid metabolism in macrophages varies depending on the pathological context. For example, deficiency of DGAT1 improves atherosclerosis in *Apoe*^{-/-} mice [92] and DGAT1 inhibition suppresses prostate tumor growth [93], suggesting that LD formation in macrophages is a crucial step in the development of pathogenic FC-Macs and LL-TAMs.

3. FC-Macs in atherosclerosis initiation and progression

Building on the foundational role of lipid metabolism in macrophage polarization outlined above, this section examines the specific contributions of FC-Macs to the initiation and progression of atherosclerosis, a chronic inflammatory disease characterized by the accumulation of fatty deposits, immune and non-immune cells, apoptotic cells, and debris within the arterial wall, leading to plaque formation that restricts blood flow and increases the risk of cardiovascular complications. FC-Macs in this context, are key mediators of the inflammatory response and lipid clearance, contributing to all stages of plaque development, including initiation, growth, rupture, and healing of arterial lesions.

3.1. LDL uptake and foam cell formation

Atherosclerosis begins with endothelial damage in areas of altered blood flow, increasing permeability and allowing LDL to infiltrate the endothelium, where they undergo modifications such as oxidation [12, 41,94]. Inflammation is triggered by oxLDL in damaged endothelial cells, inducing local macrophage proliferation and secretion of chemokines (e.g., CCL2, CCL5, CXCL1) that bind to monocyte receptors (e.g., CCR2, CCR5, CX3CR1), promoting monocyte migration and differentiation into macrophages. Initially, macrophages uptake oxLDL as a protective mechanism to prevent lipid deposition in the arterial wall. However, as the plaque progresses, the capacity of macrophages to handle LDL becomes overwhelmed, leading to lipid accumulation and the formation of FC-Macs. This accumulation triggers pro-inflammatory activation of FC-Macs, sustaining inflammation and contributing to the

development of a pathological state [13]. FC-Macs uptake modified LDL through scavenger receptors, including SR-A, CD36, and lectin-like oxidized LDL receptor-1 (LOX-1), which play pivotal roles in driving foam cell formation, promoting inflammatory activation, and contributing to atherosclerosis progression [71]. In the context of atherosclerosis, VSMCs also accumulate lipids and contribute to the total number of foam cells within the plaque. In the presence of modified LDLs, VSMCs proliferate and migrate to the intima and transform into foam cells within the plaque of mice and humans. While the role of VSMCs in plaque progression has been recognized, how VSMCs transform into foam cells remains unclear [95].

3.2. Intracellular lipid processing

Once internalized, modified lipoproteins are transported to lysosomes within FC-Macs, where they undergo hydrolysis and esterification (Fig. 2). Excessive cholesterol impairs lysosomal function, disrupting LDL digestion and autophagic flux [96]. Lysosomal acid lipase (LIPA) converts cholesterol esters and triglycerides into free cholesterol and fatty acids, respectively, while NPC1, NPC2, LAMP1, and LAMP2 proteins facilitate the transfer of free cholesterol to the cytoplasm [74]. Free cholesterol is then transported to the cellular membrane for export or to the ER, where it is re-esterified by acetyl-coenzyme A acetyltransferase 1 (ACAT1) into cholesteryl esters for storage in LDs. However, an accumulation of free cholesterol in ER membranes can impair ACAT1-mediated esterification, leading to ER stress in FC-Macs, which, if prolonged, may result in apoptosis [75]. Excessive cholesterol in atherosclerotic plaques and within FC-Macs also leads to the formation of cholesterol crystals, both extracellularly in the plaque and intracellularly within macrophages. Cholesterol crystals, whether taken up from the plaque or formed within FC-Macs, damage lysosomes, activating the NLRP3 inflammasome and triggering the release of IL-1 β , IL-18, and other pro-inflammatory mediators that act as chemoattractants, promoting further immune cell recruitment to the site [97].

FA derived from LDL are converted into triglycerides and stored in LDs or transported to mitochondria for FAO, producing NADH, FADH₂, and acetyl-CoA, which enter the TCA cycle to generate ATP. Triglyceride synthesis relies on DGAT1 and DGAT2 (Diacylglycerol O-Acyltransferase-1 and -2), which catalyze the attachment of a fatty acyl chain to diacylglycerol (DG). In diet-induced obese mice, increasing DGAT1 expression in macrophages enhances their capacity for triglyceride storage, reducing FA-induced inflammation [98] (Fig. 2). Conversely, the sequential enzymatic activity of ATGL, hormone-sensitive lipase (HSL), and monoacylglycerol lipase (MAGL) facilitates TG hydrolysis, releasing fatty acids. Deletion of ATGL in macrophages impairs TG hydrolysis, leading to TG accumulation in LDs and reduced fatty acid availability; transplantation of ATGL-knockout bone marrow into LDL receptor-knockout mice resulted in attenuated atherosclerotic lesion formation due to decreased inflammation [78,99]. Free fatty acids are converted into fatty acyl-CoA by long-chain fatty acyl-CoA synthetase (ACSL1) and transferred to mitochondria via CPT1, which facilitates acyl group transfer to carnitine. Acyl-carnitine enters the mitochondria where Acyl-CoA is released by CPT2 to fuel FAO. Conversely, acetyl-CoA carboxylase 2 (ACC2) converts acetyl-CoA to malonyl-CoA, inhibiting CPT1. OxLDL stimulates fatty acid mitochondrial trafficking while suppressing FAO, shifting FC-Macs toward glycolysis for energy production. This suppression of FAO leads to an accumulation of long-chain fatty acids in mitochondria, increasing ROS production and promoting a pro-inflammatory phenotype in FC-Macs [100,101]. Consistently, inhibition of FAO in myeloid cells increases foam cell formation and exacerbates atherosclerosis in APOE-knockout mice [102].

3.3. Cholesterol efflux

Cholesterol efflux is critical for removing excess cholesterol from FC-Macs, preventing the harmful accumulation that drives atherosclerosis

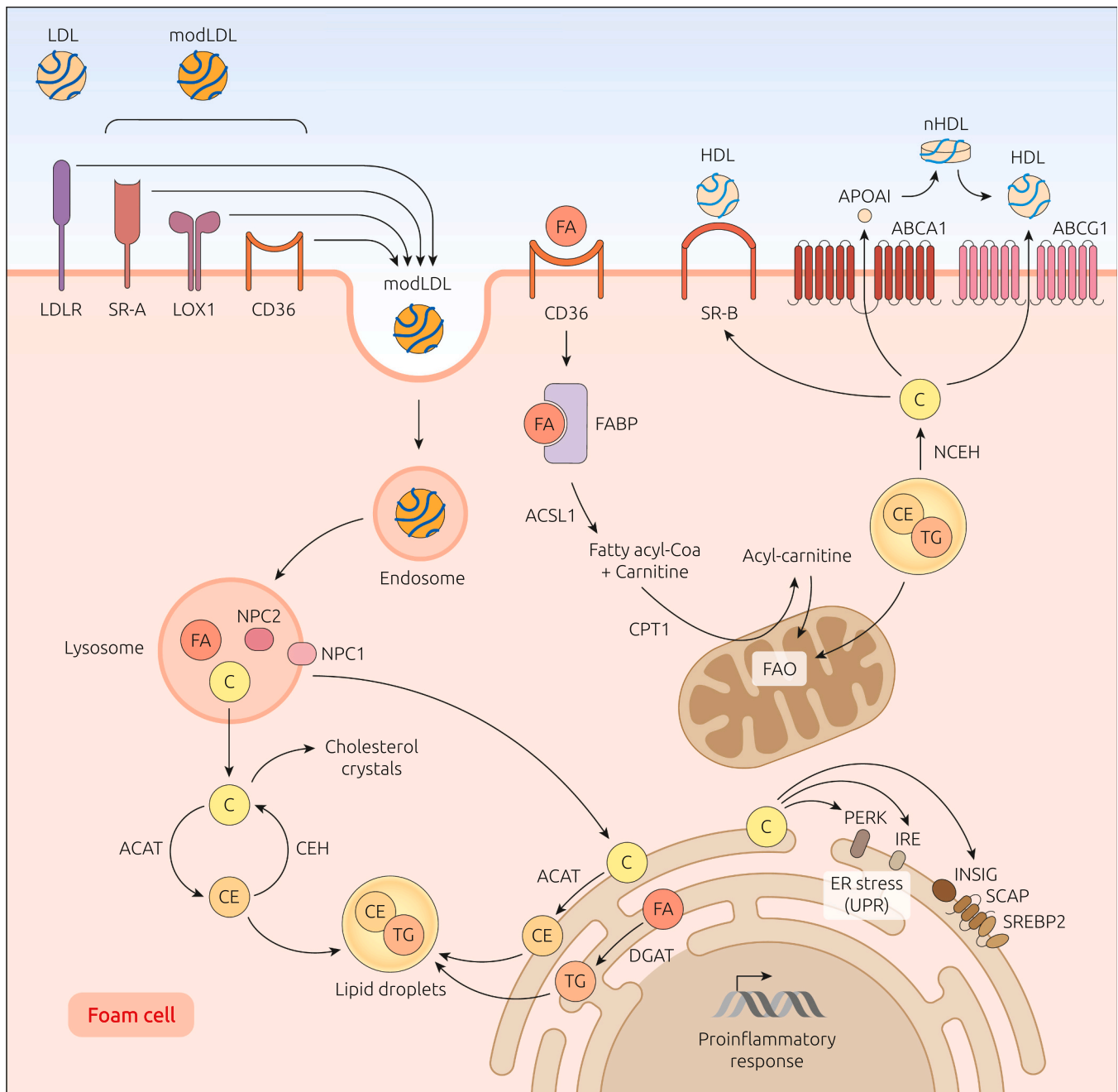


Fig. 2. Lipid metabolism in FC-Macs within the atherosclerotic plaque. Macrophages uptake modified LDL through scavenger receptors, including SR-A, CD36, and LOX-1, leading to lipid accumulation and the formation of FC-Macs. Once internalized, modified lipoproteins are transported to lysosomes, where they undergo hydrolysis and esterification. In the lysosome, NPC1 and NPC2 facilitate the transfer of free cholesterol to the cytoplasm. Free cholesterol in the cytoplasm is transported to the cellular membrane for export through ABCA1/ABCG1/SR-BI to APOAI/HDL, or to the ER, where it is re-esterified by ACAT1 into cholesteryl esters for storage in LDs. The excessive accumulation of free cholesterol in ER membranes can lead to ER stress. Excess of cholesterol in FC-Macs also leads to the formation of cholesterol crystals inducing pro-inflammatory pathways. On the other hand, fatty acids are converted into triglycerides and stored in LDs or transported to mitochondria for FAO. For initiation of FAO, free fatty acids are converted into fatty acyl-CoA by long-chain fatty acyl-CoA synthetase (ACSL1) and transferred to mitochondria via CPT1. See main text for further details.

progression. In response to excessive cholesterol, liver X receptors (LXR) are upregulated in macrophages (Fig. 2). These ligand-activated nuclear receptors, acting as sterol sensors (e.g., for oxysterols or desmosterol), promote cholesterol efflux through transcriptional activation of ABCA1 and ABCG1, while also exerting anti-inflammatory effects that integrate lipid metabolism with inflammatory responses [103]. HDL plays a central role in this process through its interaction with ABCA1, ABCG1 and SR-BI. ABCA1 mediates the transfer of cholesterol to APOAI, leading to the formation of nascent HDL (nHDL), whereas ABCG1 and

SR-BI transfer the cholesterol to more mature HDL particles. This process is essential for removing excess cholesterol from peripheral cells, which is delivered to the liver for excretion, constituting a key step in the reverse cholesterol transport pathway [104]. Macrophages with a double deficiency of ABCA1 and ABCG1 exhibit a 68–80 % reduction in cholesterol efflux to APOAI and HDL, leading to increased FC-Macs formation, NLRP3 inflammasome activation, and enhanced secretion of inflammatory cytokines [103,105–107]. LDL receptor-deficient mice transplanted with bone marrow from *Abca1*^{-/-}*Abcg1*^{-/-} mice show

accelerated atherosclerosis [106]. Consistently, myeloid LXR-deficient mice exhibit increased inflammation, FC-Macs formation, and accelerated atherosclerosis [108]. Additionally, SR-BI mediates both uptake and efflux of unesterified cholesterol between cells and HDLs. *In vivo*, bone marrow SR-BI deficiency leads to accelerated atherosclerosis [109, 110].

A key step in cholesterol efflux is the hydrolysis of intracellular cholesterol esters into free cholesterol, mediated by enzymes such as hormone-sensitive lipase (LIPE), carboxylesterase 1 (CES1), and neutral cholesterol ester hydrolase 1 (NCEH1), each playing distinct roles depending on species and cellular context [111]. Recently, LD-associated hydrolase (LDAH) has been implicated in mobilizing cholesterol ester storage in FC-Macs, activating LXR to induce cholesterol efflux and promote an anti-inflammatory phenotype, ultimately improving atherosclerosis outcomes [112].

3.4. Lipid biosynthetic pathways

Lipid homeostasis is mainly regulated by nuclear transcription factors known as SREBPs, which activate lipid synthesis under lipid-deficient conditions (Fig. 2). SREBP-2 primarily regulates genes involved in cholesterol synthesis, intracellular lipid transfer, and LDL uptake, while SREBP-1a and SREBP-1c predominantly control fatty acid biosynthesis. Under high sterol concentrations, SREBPs remain in the ER in a complex with SCAP, retained by insulin induced gene-1 (INSIG1). When sterol levels are low, SREBP matures and translocates to the nucleus to induce lipid synthesis genes. In FC-Macs, the inability to activate SREBP1 impairs the production of anti-inflammatory fatty acids, hindering inflammation resolution [69]. Additionally, desmosterol accumulation in FC-Macs induces LXR activation and inhibits SREBP, suppressing the inflammatory response [113,114]. Overexpression of 3 β -hydroxysterol Δ 24-reductase (DHCR24) in myeloid cells, which converts desmosterol to cholesterol, depletes desmosterol and promotes atherosclerosis progression [114]. Deletion of *Acly* in FC-Macs, which supports fatty acid and cholesterol synthesis, reduces desmosterol accumulation and improves plaque stabilization [115]. After nuclear translocation, SREBP regulates genes such as the LDL receptor and HMG-CoA reductase, the rate-limiting enzyme in cholesterol synthesis, further contributing to lipid accumulation in FC-Macs.

3.5. Lipid-laden macrophages in atherosclerosis regression

The mechanisms driving plaque regression are less explored than those of plaque progression. During regression, the macrophage content decreases, and anti-inflammatory macrophages predominate in the plaque, contrasting with the pro-inflammatory FC-Macs that dominate during progression. Current therapies, such as lipid-lowering through cholesterol-free diets or cholesterol-metabolizing drugs (e.g., statins, explored further in Section 6), enhance regression by reducing plaque inflammation. Increasing APOAI or HDL levels supports regression by mediating cholesterol efflux via ABCA1 and ABCG1 [41,116–118]. Inhibition of *miR-33*, a negative regulator of circulating HDL levels, drives FC-Macs toward an anti-inflammatory phenotype, enhances autophagy, facilitates cholesterol efflux, and improves efferocytic capacity, collectively contributing to plaque regression [104]. Peroxisome proliferator-activated receptor (PPAR) agonists have also been characterized by their anti-atherogenic properties [118]. Activators of PPAR- α and PPAR- γ induce cholesterol removal from human FC-Macs through stimulation of the ABCA1 pathway [119]. 2-Hydroxypropyl- β -cyclodextrin (CD) is a U.S. Food and Drug Administration (FDA)-approved substance that facilitates the solubilization of cholesterol. This mobilized cholesterol can then be hydroxylated by sterol 27-hydroxylase (CYP27A1) to form 27-hydroxycholesterol, a ligand for LXRs [120]. Activation of LXR signaling through CD upregulates target genes involved in cholesterol efflux, promotes an anti-inflammatory switch in FC-Macs, and atherosclerosis regression in ApoE $^{-/-}$ mice

[116]. Despite their therapeutic potential, LXR agonists stimulate hepatic lipogenesis, leading to hepatic steatosis and limiting their clinical applicability [121]. Some evidence showed that this adverse effect is primarily mediated through LXR α activation [122]. Current research is focused on developing LXR β -selective agonists to minimize these adverse metabolic effects [123]. Additionally, the use of macrophage-targeted nanocarriers loaded with LXR agonist represents a promising approach to reduce off-target hepatic activation [124].

The decrease in macrophage content during regression is associated with suppressed retention factors (e.g., semaphorin 3 A, netrin-1, adhesion molecules). Statins and low-density lipoprotein receptor-related protein 1 (LRP-1) deficiency promote CCR7 activation in FC-Macs [125], inducing emigration and plaque regression. Future strategies aimed at modifying FC-Macs content—by limiting recruitment, enhancing apoptosis or efferocytosis, promoting migration, or shifting toward anti-inflammatory polarization—could positively influence atherosclerosis outcomes, setting the stage for therapeutic approaches discussed in later sections.

4. LL-TAMs in cancer initiation and progression

Tumors evolve through interactions between cancer cells and immune and stromal cells within the TME [126]. TAMs in the TME exhibit dual roles—either tumor-suppressive or tumor-promoting—depending on their polarization toward an M1-like or M2-like state, respectively. M2-like TAMs promote tumor growth, metastasis, therapy resistance, and immune evasion [18]. However, scRNA-seq analyses reveal significant heterogeneity among TAM populations, often displaying mixed M1/M2 phenotypes [127]. Lipid metabolism modulates the pro-tumorigenic functions of LL-TAMs, with lipid accumulation promoting their polarization toward an M2-like phenotype [9,128].

4.1. Lipid metabolism and TAM polarization: mechanisms and functional effects

Compared to splenic or resident macrophages in healthy tissues, LL-TAMs accumulate more neutral lipids (triacylglycerols and sterol esters), leading to DGAT-dependent LD formation [129,130] (Fig. 3). In liver cancer, LL-TAMs are enriched in saturated FAs (e.g., palmitic acid, stearic acid), monounsaturated FAs (e.g., oleic acid), ω -3 polyunsaturated FAs (e.g., docosahexaenoic acid), and ω -6 polyunsaturated FAs (e.g., linoleic acid, arachidonic acid) [7,26]. Unsaturated FAs are more likely to form LDs than saturated FAs, and treatment of macrophages with docosahexaenoic or oleic acid enhances the immunosuppressive functions of LL-TAMs, decreasing T cell proliferation and IFN- γ secretion [7]. Oleic acid, other unsaturated FAs, and LD formation induce M2-like polarization through mTORC2 activation [22]. Lipid accumulation also activates PI3K- γ and upregulates PD-L1 on LL-TAMs, further promoting immunosuppression [128] (Fig. 3). Lipid accumulation in LL-TAMs and their polarization toward an M2-like phenotype are associated with a reduced capacity to phagocytose cancer cells [31,128, 131]. However, in glioblastomas, lipid accumulation in monocyte- and glia-derived macrophages occurs through the phagocytosis of cholesterol-rich myelin debris, and these LL-TAMs exhibit phagocytic signatures [21,132].

LL-TAMs uptake FAs from the TME, primarily from cancer cells, through mechanisms including passive diffusion, lipoprotein endocytosis, and active scavenging of tumor-derived vesicles via scavenger receptors such as CD36, MARCO, MSR1 (CD204, SR-A), and CD68 [129] (Fig. 3). Lipid uptake via CD36 activates p38 to suppress IFN- γ signaling, enhancing their tumor-promoting functions [133,134]. In prostate cancer, IL-1 β drives TAM recruitment and lipid accumulation via MARCO upregulation [23].

After uptake by LL-TAMs, FAs are esterified by acyl-CoA synthetases into fatty acyl-CoA, which LL-TAMs use for energy production via FAO or to build structural lipids. FAO is required for M2-like LL-TAMs to

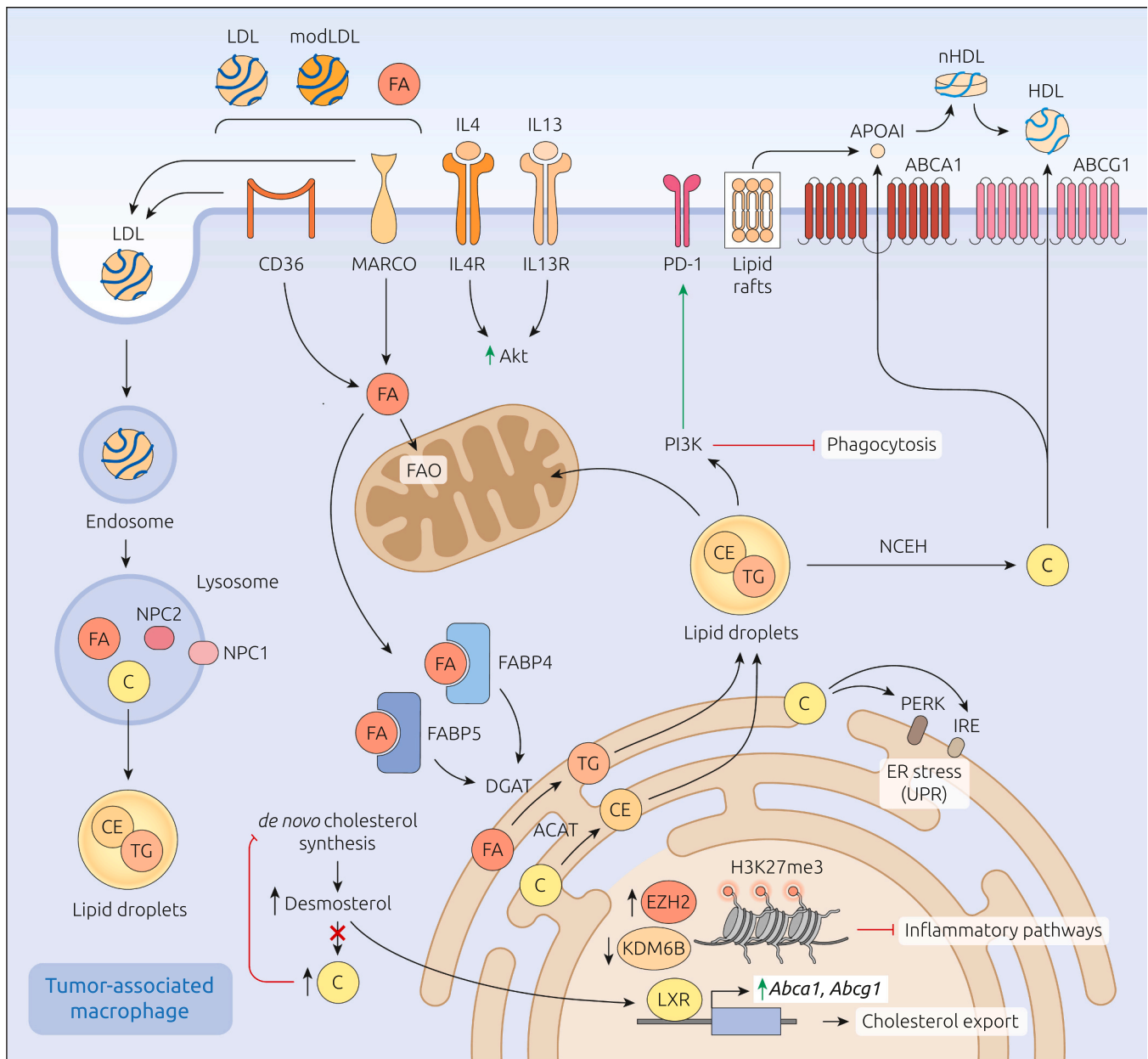


Fig. 3. LL-TAMs acquire FAs from tumor cells via passive diffusion and scavenger receptors (e.g., CD36, MARCO). FAs are esterified for β -oxidation or lipid synthesis, and transported by FABPs to activate PPAR γ -driven immunosuppressive reprogramming. Unsaturated FAs promote DGAT-dependent LD formation and M2-like polarization. Lipid accumulation activates PI3K- γ and PD-1, suppressing immune responses. It also inhibits cholesterol biosynthesis, increasing precursors that activate LXR and induce ABCA1/ABCG1, supporting tumor growth. Excess saturated FAs trigger ER stress and UPR, reinforcing immunosuppression. See main text for further details.

promote cancer cell migration and invasiveness via an IL-1 β -dependent mechanism [135]. Blocking FAO impairs LL-TAM tumor-promoting activity [129]. Similarly, RIPK3 deficiency inhibits FAO in LL-TAMs, hindering PPAR activation and reducing their pro-tumorigenic functions [136]. In LL-TAMs, FAs bind to FABPs, particularly FABP4 and FABP5, which transport them to the nucleus, promoting PPAR γ nuclear accumulation and PPAR γ -dependent M2-like polarization and immunosuppressive reprogramming [137] (Fig. 3). In breast carcinomas, FABP4 upregulation is associated with increased metastatic behavior [138].

IL-4 and IL-13 induce the phosphorylation of STAT6, which translocates to the nucleus and promotes the transcription of PPAR γ and PPAR δ [139,140]. PPAR δ functions as a fatty acid sensor and induces Arg1 and M2 polarization. Additionally, PPAR γ induces FAO and

biogenesis of mitochondria [139]. Caspase-1 inactivates medium-chain acyl-CoA dehydrogenase (MCAD) by cleaving PPAR γ , promoting lipid accumulation and TAM differentiation [141]. Conversely, enhancing MCAD activity suppresses tumor growth in mouse models.

UPR signaling and IRE1 α -XBP1 activation in cancer cells indirectly induce immunosuppression by upregulating cholesterol synthesis and promoting its secretion via extracellular vesicles [142] (Fig. 3). The UPR response in LL-TAMs is triggered not only by protein misfolding but also by lipid alterations—such as increased saturated acyl chains—which disrupt ER membrane fluidity and activate IRE1 α and PERK [143]. Unlike UPR activation due to unfolded protein overload, IRE1 α activation by lipid saturation promotes cell survival rather than triggering apoptosis [144]. ER stress in cancer cells can also transmit UPR signals to LL-TAMs via soluble factors, inducing TLR4-mediated upregulation of

UPR markers [145]. In LL-TAMs, UPR signaling additionally activates the synthesis of bioactive lipids such as sphingolipids and ceramides, further amplifying UPR signaling within the TME [146,147].

In glioblastoma LL-TAMs, lipid accumulation downregulates *de novo* cholesterol biosynthesis, leading to the accumulation of cholesterol precursors such as desmosterol. This, in turn, activates the LXR pathway and promotes cholesterol efflux (via APOA1, nHDL, and HDL) through the upregulation of ABCA1 and ABCG1 transporters [21] (Fig. 3).

Lipid efflux also influences LL-TAM polarization. In mice with a deletion of *ABCG1*, TAMs polarize toward an M1-like phenotype, reducing melanoma growth [148]. Hyaluronic acid from cancer cells triggers cholesterol efflux from LL-TAM plasma membranes, leading to the loss of lipid rafts, promoting IL-4 signaling, inhibiting IFN- γ signaling, and activating PI3K and mTORC2, thereby reprogramming LL-TAMs toward a pro-tumorigenic phenotype [149] (Fig. 3).

Cancer cells also promote *de novo* lipid biosynthesis in LL-TAMs. Lactate and other cancer cell-derived mediators transcriptionally induce fatty acid synthesis in LL-TAMs, upregulating glycerophospholipids and sphingomyelins [150]. Unsaturated FAs induce FABP4 nuclear translocation and CEBP α -mediated transcription of triglyceride biosynthesis enzymes (e.g., GPAM1, DGATs), promoting LD formation critical for maintaining LL-TAM immunosuppressive functions [26].

4.2. Interactions of LL-TAMs with cancer cells and other components of the TME in tumor progression and immunosuppression

Lipids are key mediators of paracrine communication between

tumors and their TME, including LL-TAMs [19] (Fig. 4). In glioblastoma and various carcinomas—such as colon, hepatocellular, breast, prostate, and ovarian, but notably not in gastroesophageal cancer—LL-TAM-enriched TMEs are associated with enhanced tumor progression and immunosuppression [9,20,21,23,136]. Lipid metabolism plays a central role in LL-TAM activation and function, driving tumor progression by promoting cancer cell growth, angiogenesis, metastasis, immune evasion, and suppression of anti-tumor immunity (Fig. 4).

Cholesterol derived from LL-TAMs activates pro-tumorigenic signaling pathways in cancer cells. In prostate cancer, MARCO expression in LL-TAMs correlates with poor prognosis, while LL-TAM-secreted CCL6 promotes cancer cell migration and metastasis. Blocking MARCO reduces lipid accumulation, tumor growth, and invasiveness [23]. In glioblastoma, LDs in LL-TAMs are associated with reduced phagocytic activity, dedifferentiated EMT phenotypes in cancer cells, and increased tumor angiogenesis [20,21]. Cholesterol efflux via ABCA1 and ABCG1 from monocyte- and glia-derived LL-TAMs supports the metabolic demands and proliferation of glioblastoma cells. Inhibiting LD formation or lipid metabolism in LL-TAMs disrupts these tumor-supportive functions [20,21]. Activation of the FABP4/CEBP α pathway in LL-TAMs drives lipolysis, supplying free FA that enhance cancer cell migration and metastasis *in vivo* [26]. The pro-tumorigenic phenotype of LL-TAMs in glioblastoma is also epigenetically regulated through downregulation of KDM6B and upregulation of EZH2, which increase H3K27me3 repressive histone marks and reduce chromatin accessibility at pro-inflammatory gene loci [21]. In addition, the accumulation of cholesterol precursors such as desmosterol activates LXR, inducing ABCA1 and ABCG1 expression and facilitating lipid transfer that

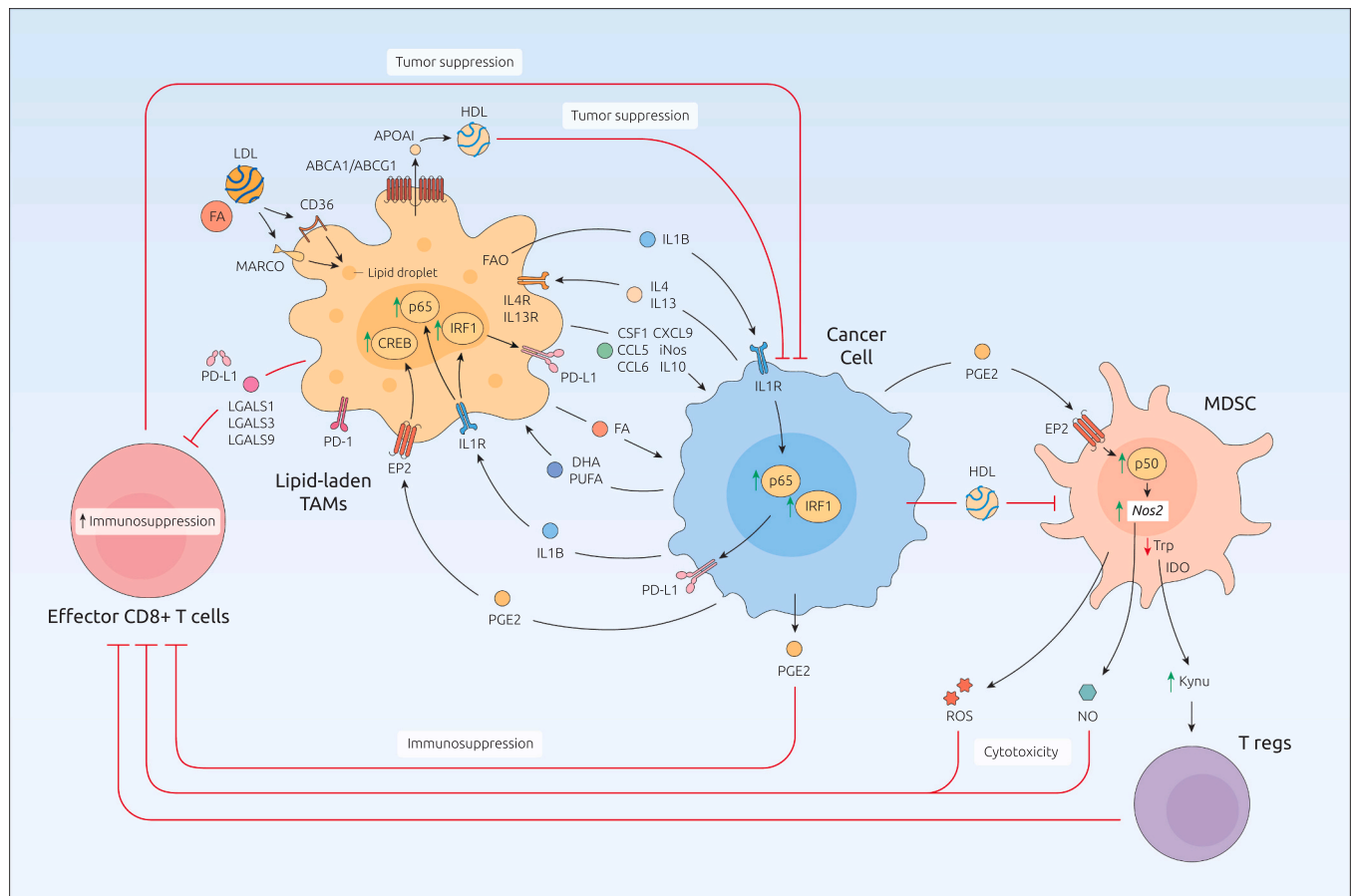


Fig. 4. LDL efflux from LL-TAMs via lipid rafts supports cancer cell metabolism and proliferation. APOA1/HDL efflux from LL-TAMs via ABCA1/ABCG1 inhibits tumor growth. LL-TAMs also secrete immunosuppressive mediators (e.g., PD-L1, LGALS1, LGALS3, LGALS9) that inhibit CD8⁺ T cell activation. In turn, cancer cells release FA and PGE2, promoting M2-like polarization and PD-L1 expression in LL-TAMs. Tumor-derived PGE2 further expands MDSCs and induces nuclear p50 NF- κ B in monocytic MDSCs, driving NO-dependent immunosuppression. See main text for further details.

sustains glioblastoma cell growth [21].

LL-TAMs also play an active role in promoting immunosuppression within the TME [9,20,21,23,136] (Fig. 4). Lipid accumulation in LL-TAMs not only reinforces their M2-like phenotype but also influences other immune cells, contributing to tumor immune evasion. Specifically, LL-TAMs suppress the anti-tumor functions of T cells, NK cells, and neutrophils through the release of immunosuppressive cytokines and the expression of immune checkpoint ligands [20,22,23,137] (Fig. 4). Exosomes released from PD-L1⁺ LL-TAMs promote CD8⁺ T cell exhaustion by upregulating PPAR α and CPT1A, thereby enhancing endogenous FAO [127]. In immunotherapy-resistant tumors, LL-TAM-derived PGE2 impairs IFN-driven activation of monocytes and dendritic cells (DCs); however, pharmacological inhibition or genetic ablation of Ptg1 and Ptg2—key enzymes in PGE2 synthesis—restores IFN responsiveness and enables CD8⁺ T cells to overcome melanoma resistance [151]. In hepatocellular carcinoma, a distinct LL-TAM subcluster expressing high levels of FABP5, scavenger receptors, lipid metabolism proteins, checkpoint ligands, and immunosuppressive molecules (e.g., FABP4, CD36, PPAR γ , ABCA1, ABCG1, PD-L1, CRLF2) supports tumor progression [137]. Targeted deletion of FABP5 or PPAR γ in LL-TAMs reduces the expression of immunosuppressive mediators (e.g., PD-L1, PD-L2, LGALS1, LGALS3, LGALS9), enhances T cell activation, and delays tumor growth [137]. Similarly, in colon cancer, LL-TAMs with high ABHD5 (a triglyceride lipolysis regulator and ATGL activator) and low MAGL levels accumulate excess lipids and promote immune evasion via the CB2/TLR4 pathway, leading to suppression of CD8⁺ T cell responses [152].

Cancer cells with elevated MAGL-dependent neutral lipolysis release free FAs into the TME, which are subsequently taken up by LL-TAMs to support their immunosuppressive function [129]. In parallel, cancer cells secrete the eicosanoid PGE2, which binds to EP receptors on LL-TAMs, promoting immunosuppression by inducing CREB1-mediated PD-L1 expression and driving an M2-like phenotype [153–157] (Fig. 4). PD-L1 expression in LL-TAMs is further upregulated by tumor-derived IL-1 through activation of IRF1 and p50 NF- κ B signaling. In LL-TAMs infiltrating liver, lung, and ovarian carcinomas, arachidonic acid metabolism shifts from the COX2/PGE2 axis toward lipoxygenase pathways, leading to increased production of 5-HETE and leukotrienes. This metabolic reprogramming is associated with elevated expression of CCL2, which sustains chronic inflammation, and IL-10, which reinforces immunosuppression [158–160]. In addition, tumor-derived PGE2 promotes the expansion of MDSCs and activates nuclear p50 NF- κ B signaling in monocytic MDSCs, resulting in NOS2 induction and NO-mediated immunosuppression [161] (Fig. 4).

Lipid metabolism in LL-TAMs is also influenced by signals from other immune and non-immune cells within the TME. In melanomas and colorectal carcinomas, for instance, Treg-mediated suppression of CD8⁺ T cells reduces IFN- γ production, which in turn activates SREBP1-dependent FAS and LD formation in LL-TAMs [162]. Cancer-associated adipocytes (CAAs) supply FA that are taken up by LL-TAMs to support their pro-tumorigenic functions [163]. Additionally, oxLDL released by PMN-MDSCs promotes immunosuppressive activity in LL-TAMs [164].

5. Gene signatures of LL-Macs in atherosclerosis and cancer

FC-Macs in atherosclerosis and LL-TAMs in cancer share a common phenotype of lipid accumulation, but their roles in disease initiation and progression are shaped by distinct microenvironmental cues. scRNA-seq and other high-throughput analyses have revealed distinct transcriptional profiles for these macrophage populations, providing insights into the molecular programs that govern their functions. Patients with atherosclerotic vascular disease—particularly those without coexisting non-atherosclerotic vascular conditions—have a higher risk of developing several cancer types, including lung, brain, liver, kidney, pancreas, and various other solid and hematologic malignancies [165];

reviewed in [33–34].

To investigate shared and divergent transcriptional features, we used the 23 TAM subpopulations identified across 17 cancer types by Coulton et al. [166] as a reference to analyze three scRNA-seq datasets from macrophages in patients with atherosclerosis [16,167–169] (Fig. 5A). Among the identified subpopulations, cluster 16—enriched in lipid metabolism-related genes—was the most expanded in atherosclerotic macrophages relative to normal carotids, accounting for 21.3 % of all macrophages in diseased tissue. Similarly, cluster 16 gene expression was elevated in LL-TAMs compared to macrophages from adjacent non-tumor areas (Fig. 5B). In both conditions, expression of lipid metabolism genes (*FABP5*, *CD36*, *MARCO*, *CD68*, *PLIN2*, *LIPA*, *APOE*, and *LAMP1*) was higher in cluster 16 than in other clusters (Fig. 5C). In TAMs, inflammation-related genes such as *MMP9* were also more highly expressed in cluster 16, whereas in atherosclerotic plaques, *MMP9* expression remained relatively uniform across clusters. *TREM2*—a receptor that promotes foam cell survival and lipid uptake while restraining inflammation [170]—was enriched in cluster 16 macrophages in both atherosclerosis and cancer, where its expression is linked to TME immunosuppression [171] (Fig. 5D). Consistent with previous studies [9,20–23,30,137], TAMs exhibited enrichment of immunosuppressive genes (*LGALS1*, *LGALS3*) in cluster 16, while genes related to immune competence (*HLA-DPA1*, *HLA-DRB1*) were reduced. A similar pattern was observed in atherosclerotic macrophages (Fig. 5C).

Despite these shared transcriptional programs, the contrasting microenvironments of atherosclerosis and cancer give rise to distinct gene expression signatures. In atherosclerosis, FC-Macs are exposed to systemic dyslipidemia and oxidative stress, leading to foam cell formation and induction of pro-inflammatory genes. In contrast, TAMs are influenced by tumor-derived signals, hypoxia, and immune suppression, resulting in gene expression profiles that promote tumor progression. Accordingly, M2-like markers such as *MRC1/CD206* were more prominent in cluster 16 TAMs, but less so in atherosclerotic macrophages (Fig. 5D). Conversely, the scavenger receptor *MARCO* was more strongly upregulated in cluster 16 macrophages from atherosclerotic plaques than in TAMs.

Together, these findings suggest that while FC-Macs and LL-TAMs share a lipid-associated core transcriptional program, they diverge in function and inflammatory tone according to their disease context. Leveraging this knowledge could inform the development of precision therapies that target shared lipid-driven mechanisms while accounting for disease-specific features—potentially enabling drug repurposing from atherosclerosis to cancer.

6. Lipid metabolism and LL-Macs as therapeutic targets in atherosclerosis and cancer

The shared gene signatures between FC-Macs in atherosclerosis and LL-TAMs, as discussed above, suggest that targeting lipid uptake and metabolism could offer therapeutic benefits in both atherosclerosis and cancer. Lipid-lowering drugs originally developed for atherosclerosis could potentially be repurposed for cancer, offering a promising strategy to enhance cancer immunotherapies and complement existing approaches such as immune checkpoint inhibitors. Some of these compounds have been evaluated in preclinical cancer models (e.g., cell lines and mouse models) and in cancer patients, but the results have been mixed. While some have been shown to inhibit cancer cell proliferation and promote apoptosis *in vitro*, as well as reduce tumor growth in mouse models, their effects in clinical studies remain inconclusive (Table 1) [28,29,172,173]. While epidemiological studies have reported reduced cancer incidence and mortality across several tumor types, interventional and randomized clinical trials have often failed to replicate these findings—and in some cases, have reported contradictory outcomes [28, 29,173; and reviewed in 172] (Table 1).

Most atherosclerosis drugs target cholesterol synthesis and dyslipidemia, while others act on LDL and VLDL aggregation, oxidation, or

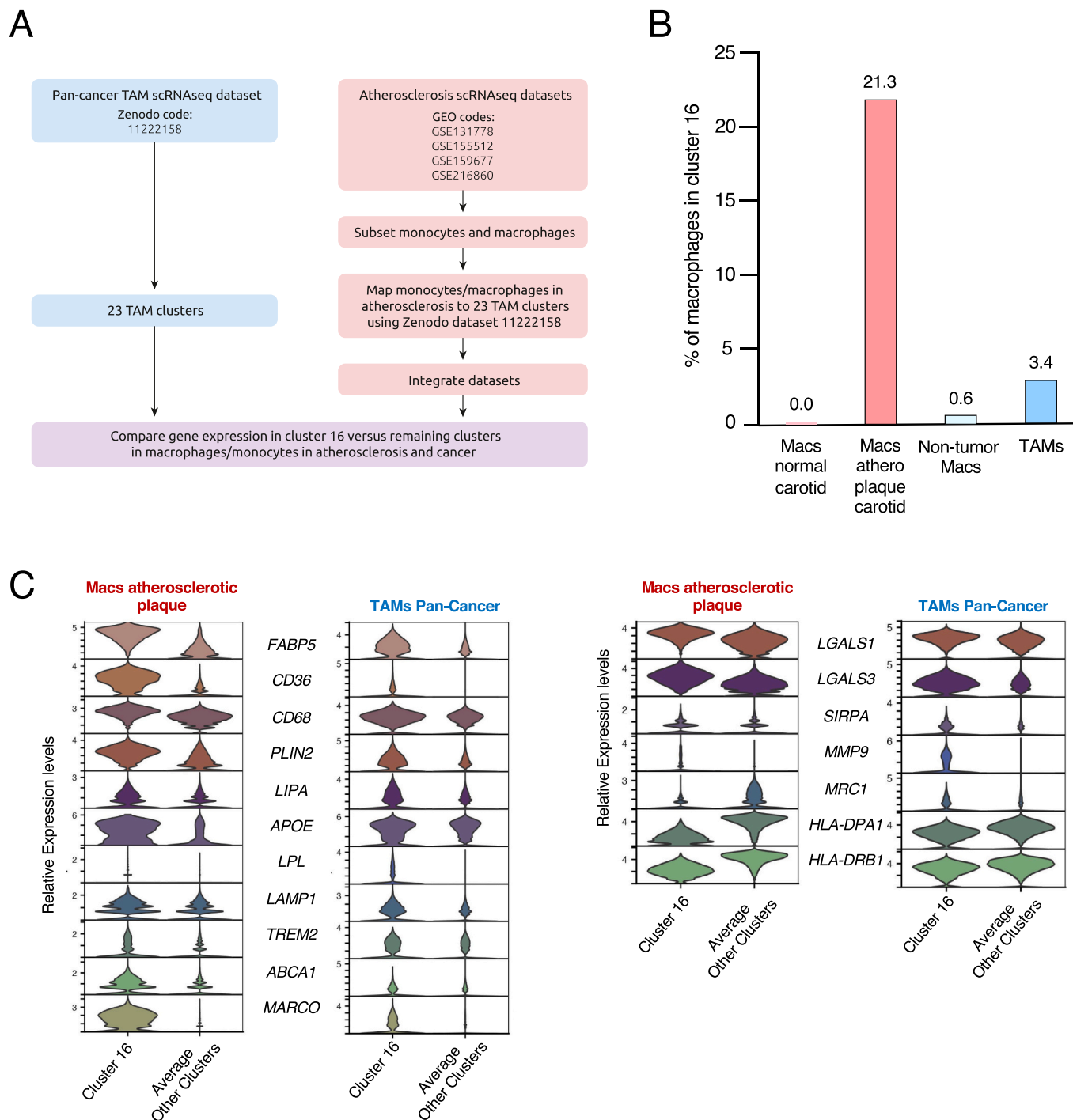


Fig. 5. Comparison of transcriptomics in macrophages in atherosclerosis and cancer. (A) Workflow of the analysis. Datasets were downloaded from GEO and Zenodo. The R package Seurat (version 5.2.1) was used to load the scRNA-seq datasets individually. For quality control, the DecontX function from the R package celda (version 1.20.0) was used to filter out ambient RNA reads. The R package scDblFinder (version 1.18.0) was applied to remove doublets. SCT transformation was performed to normalize the raw count data. The R packages Seurat and scRNAutils (version 0.0.1) were used for standard downstream analysis. SingleR (version 2.6.0) was used for cell type annotation. SCT-transformed datasets were integrated using the anchor-based RPCA method in the Seurat pipeline to remove batch effects across different datasets. Data visualization was primarily performed using Seurat and ggplot2 (version 3.5.1). The references for the scRNA-seq datasets and the code used in our analysis are publicly available on GitHub: <https://github.com/idibaps001/Review2025/tree/main>. (B) Percentage of cells in cluster 16 relative to the total number of cells across other clusters, in macrophages and monocytes from normal and atherosclerotic carotids, as well as from non-tumor and tumor areas. (C) Expression of selected lipid-related genes in cluster 16 versus the aggregate of other clusters, in macrophages and TAMs from atherosclerosis and cancer datasets. (D) Expression of other selected genes in cluster 16 versus the aggregate of other clusters, in macrophages and TAMs from atherosclerosis and cancer datasets. See main text for further details.

modification. Lipid-lowering agents include, among others, inhibitors of lipid biosynthesis enzymes (e.g., statins, bempedoic acid), cholesterol absorption inhibitors (e.g., ezetimibe), fibric acid derivatives (e.g.,

fibrates), PCSK9 inhibitors, and bile acid sequestrants. Although these drugs have been extensively studied in preclinical models and clinical trials for cardiovascular diseases, research on their anti-tumor effects

Table 1

Drugs and compounds in atherosclerosis and cancer.

Drug	Atherosclerosis		Cancer		
	Effects in preclinical models and patients with Atherosclerosis	Effects on FC-Macs	Effects in cancer cell lines and mouse cancer models	Effects in cancer patients	Effects in LL-TAMs
Statins	atherosclerotic plaque calcification [196]	Suppress uptake of oxLDL [193], Inhibit macrophage proliferation [195], enhance autophagy induced by oxLDL [194]	Inhibit the proliferation of cancer cell lines [236–238]	Improved survival across diverse advanced-stage cancers (173,176–185, 239). No survival benefit (186, 188–192)	Statins ↓ CD68*CD163* TAMs in human lung adenocarcinoma [199] TAM re-polarization by enhanced IL–10↓, IFN-γ↑, PD-L1↓ [197,200–202] Reduce oxidative stress in TAMs [198] Restored impaired M2 phagocytosis; no change in M1/M2 polarization or cytokine release in murine TAMs [204]
Bempedoic acid	Reduced cholesterol and triglyceride levels in serum and liver [240, 241]. Reduction of atherosclerotic lesions [241] Reduces LDL and improves major cardiovascular outcomes [242]	Enhanced lipid metabolism through AMPK activation [7]. Overall LDL and hsCRP lowering, reducing foam cell formation [242,243]	Inhibition of invasiveness and induced apoptosis in breast and pancreatic cancer cells [203]	N/A	
Cholesterol biogenesis inhibitors	RO 48–8071, reduction of Intestinal cholesterol and sterol biosynthesis [244] <u>Zaragozic acid</u> , reduction of hepatic cholesterol, increased expression of LDLR [245] <u>Avasimibe</u> , Reduced cholesterol levels and atherosclerotic plaque formation, reduced macrophage infiltration and MMP activity [246, 247]	<u>Zaragozic acid</u> , reduction of cholesterol synthesis in macrophages [245] <u>Avasimibe</u> , Reduction of cholesteryl esters accumulation in macrophages [248]	RO 48–8071 reduced viability and decreases in vivo growth of prostate, breast and ovarian cancer cells [249–252] <u>Zaragozic acid</u> increased sensitization to radiotherapy in AML cells [253] inhibition of growth in vivo of subcutaneous models of LLC and lymphoma [254] reduces metastatic nodules in mouse lung metastasis model [255] <u>Avasimibe</u> Reduction of tumorigenesis in CRC [256], cell cycle arrest in bladder cancer cells [257]	N/A	N/A
Ezetimibe	Reduction cholesterol uptake in the intestine through NPC1L1 blocking [258]	Reduced FC-mac formation [208]	Reduced cancer progression, tumor growth and metastasis in mice [207]	N/A	N/A
PCSK9 inhibitors	Lower levels of LDL by increasing LDLR [259]	Decrease monocyte recruitment [210] Reduces ox-LDL-mediated cytokine production [211] Inhibited FC-mac formation [261]	Stabilizes tumor cell MHC-I, enhances CTL activity, and synergizes with immune checkpoint inhibitors across various cancer types [209] Inhibition of cancer cell proliferation in lung cancer cells [262]	N/A	PCSK9 can serve as a pivotal factor in the regulation of MHC-I recycling, T-cell receptor (TCR) recycling, and TAMs [259]
PPAR agonists	K–877 improved lipid parameters and reduced plasma levels of liver enzymes [260]			Thiazolidinediones (TZD) may reduce cancer risk in T2DM patients (dose-dependent) [263]; however other data are found no effect in prostate cancer [264]	Inhibit the immunosuppressive effects of TAMs in breast and ovarian cancers [220,221] ↑ Lipid retention, PGE ₂ , M2 phenotype (immunosuppressive) [265].
MMP9 inhibitors	Morin ↓ aortic lesion area, inhibits EndMT [266].	Reduced FC-mac formation [267]	MMP2/9 inhibitor reduced brain metastasis [268] ↓ PD-L1 expression in melanoma & lung cancer cells [269]	Most matrix MMP MMP inhibitors have failed to progress beyond phase III trials [270]	Blocks MMP–9 activation in TAM-rich environment suppresses EMT and metastasis [271]
Colchicine	23–31 % reduction in major cardiovascular events [272] Enhanced plaque stability [273]	Reduced FC-mac formation [274] reduced recruitment of neutrophils, inflammatory monocytes, and macrophages into plaques [275]	Inhibits tumor growth in liver cancer models [276] increases ROS, ER stress, and mitochondrial apoptosis in pancreatic cancer cells lines [277]	Decreased risk for several cancers in immune-mediated inflammatory diseases cohorts [278] Induces senescence and apoptosis, inhibits mitosis [279]	N/A but ↑ M1 markers, ↓ M2 markers in mouse macrophages [280]

N/A: no publications available to the best of our knowledge.

has largely been limited to investigating their impact on cancer cell proliferation, apoptosis, and angiogenesis—rather than on lipid metabolism in cancer cells or in immune and non-immune components of the tumor microenvironment (Table 1) [28,29,31].

Statins, inhibitors of HMG-CoA reductase, are widely used to manage hyperlipidemia and reduce atherosclerotic cardiovascular risk. They are also the most extensively studied lipid-lowering agents in the context of

cancer [29,173–175; and reviewed in 27] (Table 1). Numerous studies have shown that statins exert anti-cancer effects in cell lines and mouse models by inhibiting proliferation, invasiveness, metastasis, and angiogenesis, while promoting apoptosis and autophagy [29]. Most population-based observational studies suggest that statins reduce cancer risk and improve prognosis and survival in patients with several tumor types, including breast, colorectal, and hepatocellular carcinomas

[176–180]. However, findings from interventional and randomized clinical trials have been inconsistent. For example, when used as neo-adjuvant therapy before surgery in breast and prostate cancer, some studies reported reduced proliferation and increased intratumoral apoptosis [181–183]. Statins have shown potential to prolong survival and enhance therapeutic efficacy in patients with breast cancer, mesothelioma, advanced non-small cell lung cancer, hepatocellular carcinoma, chronic lymphocytic leukemia and small lymphocytic lymphoma [174,175,184–187]. Conversely, other trials found no survival benefit in breast, hepatocellular or gastric cancer and, in some instances, even reported an increased incidence of new cancer cases [186,188–192].

Beyond their effects on cancer cells, statins influence monocytes and macrophages within atherosclerotic plaques by modulating lipid metabolism. They increase IL-1 β production, suppress oxLDL uptake, inhibit macrophage proliferation, and enhance autophagy [13,193–196]. Similar immunomodulatory effects have been observed in TAMs in both mouse cancer models and cancer patients, where statins reduce oxidative stress and inhibit M2-like reprogramming of TAMs [197–202].

Bempedoic acid, an inhibitor of ACLY at that blocks cholesterol synthesis in the liver, reduces FC-Mac and plaque formation (Table 1) [reviewed in 13] and exhibits anti-tumor effects in breast and pancreatic cancer cell lines by promoting a differentiated phenotype and reducing invasiveness and viability [29,203]. However, in macrophages, bempedoic acid does not affect polarization [204]. Other drugs targeting cholesterol biogenesis (e.g., RO 48–8071, Zaragozic acid) and cholesterol esterification (e.g., Avasimibe) have been tested in preclinical cancer models, primarily affecting cancer cell proliferation and survival rather than TME lipid metabolism [28]. While zaragozic acid and avasimibe have been shown to reduce cholesterol synthesis in FC-Macs (Table 1) [reviewed in 13], to the best of our knowledge, no studies have studied their effect on LL-TAMs (Table 1). Ezetimibe, a cholesterol absorption inhibitor, blocks NPC1L1 in the small intestine to reduce dietary cholesterol uptake. In xenograft mouse models of breast, prostate, bladder, pancreatic ductal, colorectal, and renal cell carcinomas, ezetimibe has been shown to reduce tumor progression by inhibiting cancer cell proliferation, inflammation, cancer stem cell stemness, and angiogenesis. It also suppresses mTORC2 signaling and enhances CD8⁺ T cell infiltration and function [205–207]. In the context of atherosclerosis, ezetimibe reduces FC-Mac formation by inhibiting caveolin-1/MAPK signaling [208]; however, its effects on LL-TAMs have not yet been investigated.

PCSK9 inhibitors, such as alirocumab and evolocumab, increase LDL receptor levels by preventing PCSK9-mediated receptor degradation, thereby reducing circulating LDL cholesterol (Table 1). In cancer, PCSK9 promotes lysosomal degradation of MHC class I molecules, limiting intra-tumoral T cell infiltration. Conversely, PCSK9 depletion increases the CTL/Treg ratio and enhances tumor responsiveness to immune checkpoint inhibitors [209]. In atherosclerosis, PCSK9 inhibitors reduce monocyte recruitment and oxLDL-induced cytokine production *in vitro* [210,211]. In cancer models, inhibition or knockdown of PCSK9 suppresses macrophage migration and M2-like polarization of TAMs in co-culture systems and reduces tumor metastasis in xenograft models [212,213].

Fibrates (e.g., gemfibrozil, fenofibrate) are PPAR agonists used to lower serum lipid levels in metabolic syndrome, demonstrate anti-tumor effects in cancer cell lines and mouse models by inhibiting apoptosis, cell cycle progression, invasion, and metastasis [29] (Table 1). These drugs can also reduce MMP9 serum levels [214], which are associated with plaque instability [215,216], and MMP9 inhibitors have been extensively evaluated in clinical trials as anti-tumoral agents [217]. However, and to the best of our knowledge, no direct evidence links these drugs to modulation of lipid metabolism in LL-TAMs. Agonists of PPAR γ inhibit atherosclerotic plaque formation in mouse models [218,219]. PPAR γ ligands inhibit the immunosuppressive effects of TAMs in breast and

ovarian cancers [220,221]; however, there is also evidence that they can also increase the risk of some cancers [222].

In 2023, the FDA approved colchicine to reduce cardiovascular events in patients with established atherosclerosis. Beyond inhibiting β -tubulin polymerization, colchicine reduces IL-1 β production in neutrophils and monocytes by interfering with NLRP3 inflammasome formation [223] (Table 1). In cancer, colchicine shifts TAMs toward an M1-like phenotype in preclinical models [224], but there is no evidence linking these effects to modulation of LL-TAM lipid metabolism, with its primary anti-tumor role involving inflammation modulation.

In atherosclerosis, macrophage-biomimetic nanoparticles delivering anti-inflammatory drugs or genes directly to plaque FC-Macs, have been shown to reduce foam cell formation and inflammation by targeting lipid-laden cells in preclinical models of atherosclerosis [reviewed in 225–227]. In cancer, nanoparticles can be potentially used to deliver drugs that modulate lipid metabolism in LL-TAMs, such as inhibitors of fatty acid uptake (e.g., CD36 blockers, PPAR γ inhibitors, FAO inhibitors) reprogramming LL-TAMs toward an M1-like phenotype, reducing their pro-tumorigenic and immunosuppressive functions [228]. These strategies, though primarily preclinical, highlight the potential of nanoparticles to address lipid metabolism in both FC-Macs and LL-TAMs, bridging atherosclerosis and cancer therapeutics.

Analyses of the transcriptomics of atherosclerotic FC-Macs and LL-TAMs revealed shared gene expression (*FABP5*, *CD36*, *MARCO*, *CD68*, *PLIN2*, *LIPA*, *APOE*, and *LAMP1*). Inhibitors of *FABP5* (*FABP5-IN-1*, *MF6*, *ART26.12*) have been examined in various contexts, including mouse models of multiple sclerosis, peripheral neuropathy, and inflammatory bowel disease [229–231]. However, while the genetic ablation of *Fabp5* in macrophages enhances anti-tumor immunity and reduces the progression of hepatocellular carcinoma [137], it has no effect on atherosclerotic plaque formation [232]. Likewise, while inhibitors of CD36 like intermidin reduce foam cell formation and atherosclerotic plaque formation in mice [233], promote tumor growth and metastasis in preclinical models and are associated with poorer prognosis in cancer patients [234,235].

In sum, drugs and macrophage-targeted nanoparticles that have proved effective in mouse models and/or human patients with atherosclerosis hold potential for cancer therapy by targeting cancer cell proliferation, apoptosis, and immune modulation (Table 1). However, differences in lipid accumulation mechanisms, namely systemic dyslipidemia in atherosclerosis versus tumor-derived lipids in cancer, suggest that FC-Mac and LL-TAM responses to lipid-modulating therapies may vary, necessitating context-specific strategies. Current evidence predominantly focuses on cancer cell responses or general immune responses, with limited data on how these therapies modulate LL-TAMs. This may reflect either a literature gap warranting further research or an actual lack of effects on LL-TAMs.

7. Concluding remarks

This review has explored the role of FC-Macs in atherosclerosis and LL-TAMs in cancer, highlighting their shared reliance on lipid metabolism, and revealing common and distinct pathogenic mechanisms of these diseases. Across both conditions, FC-Macs and LL-TAMs exploit lipid pathways to drive cell metabolism, further disease progression, and modulate response by other immune cells, highlighting lipid metabolism as a critical determinant of macrophage function with implications for therapeutic intervention. While drugs targeting lipid metabolism show promise in modulating cancer cell behavior, the limited direct evidence for their impact on LL-TAMs underscores a critical research gap. Addressing this gap through targeted studies could unlock novel strategies to simultaneously mitigate cardiovascular and oncologic burdens, leveraging the shared biology of LL-Macs to improve patient outcomes in both diseases.

7.1. Statement on the relevance of the study for clinicians, patients, teachers, and policymakers

This review synthesizes current knowledge about LL-Macs in both pathologies while emphasizing the broader implications of macrophage lipid metabolism for human health and disease. The article has outlined the current understanding of LL-Macs as a common factor in these diseases, offering insights into their molecular mechanisms and their potential as targets for therapeutic intervention. By bridging the cardiovascular and oncologic fields, it highlights the need for interdisciplinary approaches to improve public health outcomes. To that end, the review aims to be relevant for the four groups of stakeholders: for translational researchers and clinicians by informing the development of new therapies and the repurposing of therapeutic strategies from atherosclerosis to cancer, for patients by enhancing their understanding of disease mechanisms and therapeutic options, for academics by aiding in the education of future researchers, and for policymakers by helping to shape healthcare priorities based on evidence.

CRediT authorship contribution statement

- o MC Martínez-Campanario: Conceptualization, Writing-Original draft preparation, Writing-review & editing. Figure preparation.
- o Marlies Cortes: Conceptualization, Writing-Original draft preparation, Writing-review & editing. Figure preparation.
- o Lu Han: Bioinformatics analysis for Fig. 5. Writing-review & editing. Figure preparation.
- o Agnese Brischetto: Writing-review & editing.
- o Paloma Rivero-Soriano: Writing-review & editing.
- o Joan Font-Díaz: Writing-review & editing.
- o Joan Maurel: Writing-review & editing.
- o Vicente Andrés: Writing-review & editing.
- o Antonio Postigo: Conceptualization, Writing-Original draft preparation, Writing-review & editing. Figure preparation. Funding.
- o All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no competing interests related to the content of the article.

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Data availability

Figure 5 include the link with the data source

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