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Role of lipids in the metabolism and activation of immune cells

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Abstract

Immune cell plasticity has extensive implications in the pathogenesis and resolution of metabolic disorders, cancers, autoimmune diseases and chronic inflammatory disorders. Over the past decade, nutritional status has been discovered to influence the immune response. In metabolic disorders such as obesity, immune cells interact with various classes of lipids, which are capable of controlling the plasticity of macrophages and T lymphocytes. The purpose of this review is to discuss lipids and their impact on innate and adaptive immune responses, focusing on two areas: (1) the impact of altering lipid metabolism on immune cell activation, differentiation and function and (2) the mechanism by which lipids such as cholesterol and fatty acids regulate immune cell plasticity.

Keywords

Inflammation; Macrophages; T lymphocytes; Oxysterols; Fatty acids

1. Introduction

1.1. Immune cell polarization

The immune system protects the body from infection by destruction and removal of pathogens. The innate immune system acts as the first-line defense and involves the activation and recruitment of neutrophils and macrophages that phagocytose pathogens. The adaptive immune system acts as the second line of defense by providing long-term protection from specific pathogens through the production of antigen-specific antibodies. Pathogens are presented to B and T lymphocytes as antigens. This interaction leads the activation of T cells that release cytokines and stimulates B cells to produce antibodies that aid in the recognition and killing of invading pathogens.

Immune cells are classified based on the expression of cellular markers and secretion of cytokines. During bacterial infections, macrophages are defined as either classic (M1) or alternative activated (M2). M1 macrophages function to amplify the inflammatory response through release of cytokines that recruit other immune cells to the site of inflammation. They secrete inflammatory markers interferon gamma (IFN-γ), interleukins IL-1β and IL-6, C-X-C motif chemokines CXCL10 and CXCL9 and tumor necrosis factor TNF-α. M1

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polarization is also identified by the presence of cellular makers CD319, CD274 and CD38 [1]. In contrast, M2 macrophages are involved in tissue repair and remodeling. M2 macrophages are defined by the expression of antiinflammatory markers IL-4, IL-13 and/or IL-10 and cell surface markers CD206, CD301 and CD163 [2].

Similar to macrophages, T lymphocytes secrete cytokines and soluble protein factors that suppress, activate and/or kill neighboring infected cells. T lymphocytes originate from naïve cells in the thymus that differentiate into two primary subsets of T lymphocytes and are distinguished by the presence of the cell surface markers CD8 and CD4. These cells further undergo proliferation and differentiate into effector or memory T lymphocytes. CD8 lymphocytes can differentiate into cytotoxic T lymphocytes (CTLs). CTLs induce apoptosis in targeted cells by secreting proteins, granzyme and perforin and also by inducing the Fas ligand/Fas signaling pathway [3]. CD4 effector T lymphocytes can differentiate into T helpers Th1, Th2 and Th17 or T regulatory (Tregs) lymphocytes. Similar to macrophages, Th1 lymphocytes are primarily classified as proinflammatory and defined by the secretion of IFN-γ and TNF-α [4]. Th2 lymphocytes are primarily antiinflammatory and defined by secretion of IL-13, IL-4, IL-10 and IL-5. Th17 T lymphocytes express a proinflammatory phenotype defined by the secretion of IL-17 and IL-22. Over the years, Tregs have received vast interest due to their ability to dampen inflammation [5–7]. These suppressive lymphocytes express the protein Foxp3 and CD25 and secrete cytokines such as TGF-β, IL-10 and IL-35 that directly suppress the inflammatory function of Th1, Th17, CTL and B cells [8].

1.2. Immune cell polarization in metabolic diseases

Altered lipid homeostasis underlies the etiology of some of the most common chronic diseases — obesity, cardiovascular disease (CVD) and liver disease. Not coincidentally, these conditions are also associated with chronic inflammation and inflammatory polarization of macrophages and T lymphocytes (Fig. 1). This correlation has led to much interest in understanding the impact lipids have on immune polarization and the impact immune polarization has on lipid handling in these metabolic diseases.

In 2007, Lumeng *et al.* first introduced the concept that adipose tissue macrophages (ATMs) could undergo a similar polarization as bacteriostatic macrophages [9]. In lean AT, ATMs primarily display an M2 phenotype while there are more M1 macrophages present under obese conditions. The M1 macrophages were classified as M1 because they secrete inflammatory cytokines, TNF-α and IL-1β, that further disrupt adipocyte homeostasis and perpetuate local and systemic insulin resistance [9]. This classification was considered the dogma for ATM classification. However, classifying tissue immune cell polarization based on phenotypes induced *in vitro* or during an infection does not fully portray their phenotype in other tissues [10].

In a recent study, proteomic analyses comparing ATMs from lean and obese adipose tissue (AT) introduced the concept of “metabolically activated (MMe) macrophages” in obese AT [1]. Inflammatory ATMs from obese AT were found to have a distinctly unique phenotype from M1 polarized macrophages present during bacterial infection. Macrophages acquired from bacterial infection and lipopolysaccharide (LPS)-treated macrophages express cellular

markers CD319, CD274 and CD38 that are dependent on the type I interferon signaling response [1]. In contrast, ATMs from obese individuals express lipid transport proteins ATP-binding cassette member 1 (ABCA1) and fatty acid translocase (CD36) [1]. This MMe phenotype is reproducible *in vitro* by treating macrophages with palmitate, insulin and glucose [1]. The one consistent similarity between the M1 and MMe macrophages is the secretion of proinflammatory cytokines, TNF-α, IL-6 and IL-1β. In both types, IL-1β induction was dependent on the activation of the Toll-like receptors TLR2 and TLR4 [1]. These findings demonstrate that the classic nomenclature for M1 and M2 macrophages is upheld when macrophages are classified by cytokine production, but the mechanism of activation and other aspects of the functional phenotype depend on the tissue environment and disease state.

Macrophages are similarly important in liver disease and CVD. Much like the lean-to-obese adipose tissue transition, macrophages play an important role in the pathogenesis of chronic liver injury and nonalcoholic fatty liver disease (NAFLD). There are two main types of macrophages in the liver — embryonic-derived Kupffer cells and monocyte-derived $CD11b^{+}Ly6C^{+}$ macrophages [11]. Kupffer cells sense tissue injury and are responsible for initiating inflammatory stimuli. The $Ly6C^{hi}$ monocytes are recruited by CCR2-dependent mechanisms [12,13]. The conversion of $Ly6C^{hi}$ monocytes to macrophages promotes resolution of inflammation and regression of fibrosis [14–16].

Monocyte-derived macrophages are the primary immune cell to accumulate in atherosclerotic plaques [17]. The mere accumulation of macrophages in plaques increases the vulnerability of plaques to rupture. Both M1 and M2 polarized macrophages are present in plaques, although the importance of their relative ratios *in vivo* is still not well understood [18–20]. With regard to lipids, cholesterol efflux from macrophages is important for resolution of atherosclerosis. In early atherosclerotic plaques, monocytes that are differentiating into macrophages become cholesterol laden foam cells but undergo clearance via efferocytosis [21]. This resolves the inflammation in the plaque. In an advanced cell, efferocytosis declines and, under inflammatory stimuli, apoptotic macrophages become necrotic. Necrosis of macrophages induces degradation of the collagenous fibrous cap over the plaque and rupture [21,22].

Much like macrophages, Th1 lymphocytes are more prevalent in metabolic tissues (AT, liver) in disorders such as obesity, diabetes and CVD. CD4 Th1 lymphocytes are elevated in visceral fat and act as a major regulator of insulin resistance [23]. In contrast, CD4 Th2 lymphocytes protect against diet-induced obesity and insulin resistance. Th17 cells are key players in the development of hypertension [24], Crohn’s disease [25] and rheumatoid arthritis [26].

Macrophages and T lymphocytes interact with a number of intrinsic and extrinsic factors that influence their proliferation and differentiation. Immune cell function and phenotype is dependent on the microenvironment and varies based on the tissue environment in the disease state. Lipids and alterations in lipid metabolism have been recently identified as regulators of immune cell polarization. The following sections will discuss how lipids

regulate immune cell polarization and highlight the immune cell interactions with various lipid classes and activation of transcription factors that control lipid metabolism.

2. Impact of lipids on macrophage and T lymphocyte phenotypes

2.1. Sterols and oxysterols

Cellular cholesterol homeostasis is primarily regulated by the competing transcription factors sterol receptor element binding protein (SREBP) and liver X receptor (LXR). Sterols and oxysterols have received considerable interest in recent years because they are ligands of SREBP and LXR, are elevated in metabolic disorders, and can influence immune cell function.

Oxysterols 27-hydroxycholesterol (27HC), 25-hydroxycholesterol (25HC) and 24*S*-hydroxycholesterol are cholesterol precursors. In NAFLD, 27HC has been shown to promote an antiinflammatory phenotype in Kupffer cells. The enzyme cytochrome P450 family 27 subfamily A polypeptide 1 (CYP27a1) is responsible for the production of the 27HC. Knockdown of CYP27a1 increases hepatic inflammation. Likewise, administration of 27HC or overexpression of CYP27a1 in hematopoietic cells reduces hepatic inflammation and lipid accumulation in Kupffer cells [27,28]. 27HC also induces an M2 phenotype in Kupffer cells by interacting with Niemann-Pick type C1 (NPC1) proteins, which are necessary for the transport of intercellular cholesterol to cytosol [27].

27HC is one of the most abundant oxysterols found in atherosclerotic plaques and serum levels positively correlate with hypercholesterolemia and age [29]. In contrast to its effects on NAFLD, 27HC is proatherogenic in CVD and induces an inflammatory phenotype in vascular macrophages. 27HC is metabolized by the cytochrome P450 family 27 subfamily B polypeptide 1 (CYP7B1). Knockdown of CYP7B1 in an apolipoprotein E (apoE) atherosclerotic mouse model leads to elevated inflammation and accelerated atherosclerotic lesion formation [33]. Similarly, *in vitro* studies have shown that direct treatment of macrophages with 27HC increases IL-6, TNF-α and IL-1β expression [34–36]. Mechanistically, 27HC drives the M1 phenotype in macrophages through the estrogen receptor alpha [30]. It is not well understood why oxysterols induce inflammation in arterial associated macrophages and employs an antiinflammatory phenotype in Kupffer cells. These differences suggest tissue specificity in response to oxysterols. In liver and cardiovascular tissue, different subclasses of macrophages are present [11,18–20]. Thus oxysterols may drive an antiinflammatory phenotype in a specific type of macrophage via LXR, while they induce inflammation in a different subset of macrophages through LXR-independent pathways, such as the estrogen receptor [30].

Desmosterol is the most prevalent sterol in atherosclerotic plaques and is a ligand for both LXR and SREBP [31–34]. When macrophages have elevated intracellular cholesterol, desmosterol metabolism is inhibited, leading to elevated desmesterol. Studies have shown that treating macrophages with desmesterol not only induces the expression of cholesterol efflux genes but also suppresses inflammatory genes (Cxcl9 and Cxcl10) [31]. Thus, desmosterol contributes to the low inflammatory state of cholesterol-laden macrophages.

In disease states like atherosclerosis, the high levels of cholesterol in macrophages can also cause mitochondrial dysfunction, contributing to inflammatory stimulation. Mitochondrial cholesterol accumulation leads to mitochondrial uncoupling by opening of the permeability transition pore and mitochondrial cholesterol trafficking complex [35]. In this state, excess cholesterol can be metabolized by CYP27A1, resulting in increased amounts of oxysterol. These oxysterols then become esterified and are thereafter unable to bind LXR [35]. Thus, they lose their antiinflammatory capabilities and only contribute to mitochondrial uncoupling.

Oxysterols (27HC, 7β-2HC and 7-keto-27HC) are also potent activators of the orphan nuclear receptor RAR-related orphan receptor gamma t (RORγτ) on T lymphocytes [36]. Activation of RORγτ is important for IL-17 production by CD4 T lymphocytes. Mice without CYP27a1, the enzyme responsible for the production of oxysterols, have low levels of IL-17 production. Treatment with oxysterols increases IL-17 production. These studies suggest that the effect of oxysterols on immune cells differs from tissue and disease state and likely depends on specific receptor binding.

2.2. Saturated fatty acids

Fatty acids are a major fuel source for cellular activity and serve as the backbone for cell membrane phospholipids and glycolipids. Elevated dietary intake of saturated fatty acids (SFAs), palmitate and stearate, is strongly correlated with inflammation and the metabolic syndrome [37–40]. In contrast, unsaturated fatty acids (oleate and linoleate), particularly polyunsaturated fatty acids (PUFAs), may prevent or resolve inflammation.

When Kratz *et al.* developed the MMe *in vitro* model, the SFA palmitate, not glucose or insulin, was sufficient to induce the inflammatory and metabolic phenotype of ATMs in obese AT [1]. Palmitate induces macrophages to express inflammatory cytokines by activating the nuclear receptor NFκB, a master regulator of inflammation [41]. Stearic or palmitate acid can also bind TLRs to activate JNK and NFκB pathways, inducing the up-regulation of MCP-1, IL-1β and TNF-α. Scavenging activity by macrophages can lead to the intracellular accumulation of SFAs and other lipids such as diacylglycerols (DAGs). The accumulation of SFAs and DAGs can be toxic by inducing endoplasmic reticulum stress, which also drives the inflammatory M1 phenotype in macrophages [42,43].

Even though fatty acids are good respiratory substrates for mitochondria, excess fatty acids can lead to mitochondrial dysfunction and thereby contribute to macrophage inflammation. SFAs can increase conductance of the mitochondrial membrane and induce uncoupling [44]. The increased length of the hydrocarbon chain in SFAs along with absence of double bonds increases the capacity to depolarize mitochondria [44]. For example, treating foam cells in CVD with SFAs (oxalic acid, linoleic acid and arachidonic acid) not only induces the uncoupling protein UCP2 but also IL-1α production by macrophages [45].

Similar to macrophages, CD4 T lymphocytes treated with increasing concentrations of palmitate are induced to secrete proinflammatory cytokines (TNF-α, IL-1β and IL-6) and have oxidative stress [46]. Elevated concentrations of palmitate increase T lymphocyte expression of inflammatory markers CD69, IL-2 and the insulin receptor. This phenotype

was induced by palmitate, as treatment with the unsaturated fatty acids linolenic acid had no effect on CD4 T lymphocytes. The impact of SFAs on T cell function and activation has been extensively reviewed by Jong *et al.*[47].

Short-chain fatty acids (SCFAs) can also regulate T lymphocyte activation and differentiation and have been shown to contribute to intestinal inflammation. SCFAs, such as acetic acid, propionic acid and butyric acid, are produced by bacterial fermentation of dietary fiber in the gut. In both *in vitro* and *in vivo* studies, SCFAs increase proliferation of Tregs in the gut [48]. Likewise, SCFAs enhance Th1 and Th17 differentiation and cytokine expression (IL-10, IFN-γ and IL-17) [49]. Because SCFAs are able to signal through G-protein-coupled receptors (GPR41 and GPR43), it has been proposed that SCFAs signal through these receptors to activate T lymphocytes. However, T lymphocytes do not express functional levels of GPR41 or GPR43 [50,51] or their downstream signaling pathways [51]. When T cells are activated, they have increased histone deacetylase (HDAC) activity, which down-regulates expression of inflammatory cytokines by inhibiting mTOR-S6K and STAT3 pathways [49]. Acetate and proprionate bypass GPCRs and inhibit HDAC, leading to increased expression of inflammatory cytokines (IL-17, IFN-γ and IL-10) in T lymphocytes. These findings correlate with previous findings that SFA and SCFAs drive an inflammatory phenotype in macrophages and T lymphocytes.

2.3. Polyunsaturated fatty acids

PUFAs, such as omega-3 and omega-6 fatty acids, are therapeutic targets for CVD and metabolic disorders because they can regulate inflammation. PUFAs are essential fatty acids; they are only available from dietary sources. Their regulatory role in inflammation was first identified when high dietary PUFA intake was correlated with low risk for CVD in humans.

The PUFAs linoleic acid, alpha-linolenic acid and docosahexaenoic acid (DHA) have been shown to blunt LPS-induced inflammation in THP-1 macrophages [52]. DHA also increases the secretion of IL-10 by acting in an autocrine manner to further reduce the expression and secretion of IL-1β and TNF-α [53]. DHA can impair NFκB, the master regulator of inflammation in macrophages, by activating PPARγ [54] and AMP-activated protein kinase (AMPK) [55]. These findings provide a mechanism by which omega-3 fatty acids regulate macrophage plasticity, driving cells toward an antiinflammatory phenotype.

Conjugated linoleic acid (CLA) is derived from linoleic acid and n-6 PUFA [56]. The cis-9, trans-11 CLA isomer is the most abundant and naturally occurring dietary form of CLA. This isomer has been extensively studied for its antiinflammatory properties. One way CLA reduces inflammation is by modulating dendritic cell migration and activation. Homing of dendritic cells to lymph nodes is important for activation of T lymphocytes and dendritic cells can secrete cytokines important for regulating the Th1 response (IL-12p40, IL-12p70 and IL-27). *In vitro* and *in vivo*, treatment with CLA impairs LPS-induced dendritic cell migration and cytokine production [57]. Treatment with CLA also reduces the expression of MHC class II and the costimulatory molecules CD80 and CD86 in resting and activated dendritic cells.

Similar to CLA, the omega-3 fatty acid, DHA, impairs MHC II and costimulatory protein expression in dendritic cells [58] and increases IL-10 secretion in T effector lymphocytes [59]. For example, dietary intake of safflower oil, which is abundant in alpha-linolenic acid and DHA, impairs IL-2 production and T lymphocyte proliferation [60,61]. DHA exerts these antiinflammatory properties by inhibiting the phosphorylation of the mitogen-activated protein p38. In proliferating cells, DHA causes cells to undergo apoptosis [62]. DHA exerts similar effects on Treg function and proliferation. Interestingly, Yessoufou *et al.* found that DHA impaired the suppressive function and migration of Tregs [59]. However, further studies are needed to address how PUFAs directly impact immune T cell plasticity. Specifically, it will be of interest to identify how PUFAs regulate ligand-receptor interactions, intracellular signaling and membrane fluidity.

3. Intersection of cellular lipid metabolism and inflammatory pathways

3.1. Impact of lipid metabolism on macrophage inflammation

Lipid metabolism consists of the production of lipid species (cholesterol, fatty acids and phospholipids) and the breakdown of lipid species via fatty acid oxidation. Transcriptional regulation of lipid metabolism is tightly controlled by SREBP and LXRs. SREBP-1a and LXRα are highly expressed in macrophages and known regulators of cytokine release from macrophages [63,64]. LPS treatment increases SREBP-1a activity and *de novo* synthesis of cholesteryl esters and triglycerides in peritoneal macrophages [65]. In support of these findings, bone-marrow-derived macrophages deficient in SREBP-1a are protected against LPS-induced IL-1β production [63]. Mechanistically, activation of SREBP-1a induces the expression of inflamma-some components, inducing the cleavage of inflammatory cytokines pro-IL-1β and pro-IL-18, which are necessary for the production of mature cytokines [66]. These findings suggest that SREBP activation is linked to an M1 phenotype (Fig. 2).

Unlike SREBP, activation of LXR is strongly linked to an M2 phenotype in macrophages. LXR regulates cholesterol homeostasis and lipid synthesis, including genes involved in lipid efflux (Abca1, Abcg1 and Apoe), cholesterol transport (Npc1 and Npc2) and fatty acid remodeling (Fads2, Scd1 and Scd2) [67]. Mice specifically lacking LXR in macrophages have accelerated atherosclerosis due to the increased accumulation of cholesterol in macrophages [68]. Overexpression or pharmacological activation of LXRα suppresses LPS-induced inflammation in macrophages [69]. Similarly, overexpression of CYP27a1, which enhances the production of 27HC, a ligand for LXRα, leads to increased expression of LXRα and results in the reduction of LPS-induced TNF-α expression in macrophages [28]. LXR dampens inflammation through transrepression by forming a hetero-dimer with RXR and inducing corepressors NCoR and SMRT [70]. Together these factors inhibit the activity of the inflammation associated transcription factors NFκB and AP-1, that are largely known to induce the M1 phenotype [70]. The function of LXR in immune cells has also been extensively reviewed in Spann *et al.*[71].

Enhanced β-oxidation of lipids can also induce an antiinflammatory phenotype in macrophages. AMPK increases β-oxidation by inhibiting the activity of acetyl-coA carboxylase (ACC) through phosphorylation [72]. ACC converts acetyl CoA into malonyl CoA, required for the generation of acetyl groups necessary for fatty acid synthesis. Malonyl

CoA inhibits fatty acid flux into the mitochondria, blocking β-oxidation. By inhibiting β-oxidation, lipid species accumulate, driving the macrophage to an M1 phenotype [73,74]. AMPK-deficient macrophages are known to have reduced fatty acid oxidation, lipid accumulation and inflammation [75,76]. Treatment of macrophages with the antiinflammatory cytokine IL-10 enhances AMPK activity [77]. Under conditions of excess nutrients, such as hyperlipidemia and obesity, AMPK is inactive, allowing fatty acid synthesis to occur and leading to the accumulation of lipid intermediates and subsequent inflammation. These findings suggest that driving macrophages toward an antiinflammatory phenotype requires the breakdown and efflux of lipids through the activation of LXR and AMPK (Fig. 3). However, more studies are necessary to support these findings.

Mitochondria are also involved in lipid-metabolizing properties of macrophages — specifically, intracellular lipolysis and cholesterol flux. Altered lipid availability can lead to mitochondrial dysfunction and change the inflammatory state of macrophages. For example, macrophages became more inflammatory in the mouse knockout of Comparative Gene Identification-58 (CGI-58), a protein that mediates intracellular lipolysis [78]. Specifically, this occurred through mitochondrial dysfunction and increased reactive oxygen species, which activate the inflammasome [79]. It was further shown that LPS and SFA could inhibit CGI-58, demonstrating how these lipotoxic lipids induce macrophage inflammation via mitochondrial dysfunction [78].

3.2. Impact of T lymphocyte lipid metabolism on proliferation and activation

T lymphocyte proliferation is highly dependent on glycolysis and the degradation of lipids for energy through β-oxidation. Once activated, T lymphocytes depend primarily on glycolysis and reduce their use of β-oxidation [80]. *De novo* lipogenesis also contributes to activation of T lymphocytes. Activation of CD8 T lymphocytes occurs through the TCR-receptor-mediated protein kinase C-mTor pathway, which leads to activation of SREBP regulating genes involved with cholesterol biosynthesis (Hmgcr, Hmgcs and Sqle) and fatty acid synthesis (Acaca and Fasn) [81,82]. Deletion of the chaperone protein SCAP, which inhibits SREBP activity, reduces proliferation of activated CD8 T lymphocytes. During viral infection, lack of SREBP reduces TNF-α and IFN-γ secretion in CD8 T lymphocytes. Similarly, inactivation of ACC1, a downstream target of SREBP, impairs the ability of CD8 T lymphocytes to proliferate following infection [83]. These recent advances in lymphocyte function demonstrate that both metabolic processes, glycolysis and lipogenesis, are required for proliferation of CD8 T lymphocytes. It is speculated that T lymphocytes require lipids during proliferation to maintain and remodel cell membranes. Lipogenesis is necessary for production of phospholipids, which comprise the endoplasmic reticulum membrane and cellular membrane. However, more studies are necessary to validate this concept.

LXRα and LXRβ are expressed in T lymphocytes and important for proliferation [84,85]. In the absence of LXRβ, stimulation with mitogen stimulus anti-IgM, concanavalin A and a combination treatment of PMA and ionomycin increases splenic CD4 and CD8 T lymphocytes. Likewise, LXR ligand, 22(*R*)-hydroxycholesterol reduces T lymphocyte proliferation. During T lymphocyte activation, SREBP-1 and target genes are up-regulated while LXR-dependent genes are reduced. This occurs through induction of SULT2B1, an

enzyme responsible for oxysterol metabolism, and ABCC1, a membrane transporter that exports oxysterols. Thus lack of ligands in the form of oxysterols impairs LXR activation. Studies suggest that LXR impacts only proliferation and does not regulate activation, as LXR activation does not up-regulate activation markers CD69, CD44 and CD25 or IL-2 production.

De novo lipogenesis is required for the differentiation of Th17 lymphocytes into immunosuppressive Tregs. Berod *et al.* discovered that inhibition of ACC1 impairs the differentiation and proliferation of both mouse and human Th17 cells and pushes the cells toward a Treg phenotype [86]. ACC1 enzymatically converts acetyl CoA into malonyl CoA, which is further synthesized into palmitate. Under conditions of elevated SFAs, this process is blocked, further inducing the Th17 phenotype. These findings have implications for therapies aimed at uncontrolled proliferation of Th17 cells or toward reprogramming cells to an immunosuppressive phenotype. By regulating *de novo* lipogenesis and lipid efflux, immune cells can possibly be driven from a proinflammatory phenotype to an antiinflammatory phenotype. Regulation of these lipid pathways can occur by binding specific lipid ligands to LXR or SREBP or by lipids stimulating receptor-mediated cell signaling. In particular, cholesterol precursors and metabolites, along with fatty acids, likely control these pathways.

4. Conclusion

Recent advances delineate the integral role lipids play in regulating macrophage and T lymphocyte function and phenotype. Pathways promoting lipid synthesis and accumulation tend to drive a proinflammatory phenotype (Fig. 2) while pathways enhancing β-oxidation and lipid efflux push immune cells toward an antiinflammatory phenotype (Fig. 3). When linking various pathways to specific phenotypes in immune cells, it is important to keep in context that the environment (tissue and disease state) as the function of macrophages and T lymphocytes may differ in response to various lipids. Identifying distinct and specific pathways induced in immune cells by various lipid species could aid in the development of novel targeted therapies for treating autoimmune diseases, metabolic disorders and chronic inflammatory disorders.

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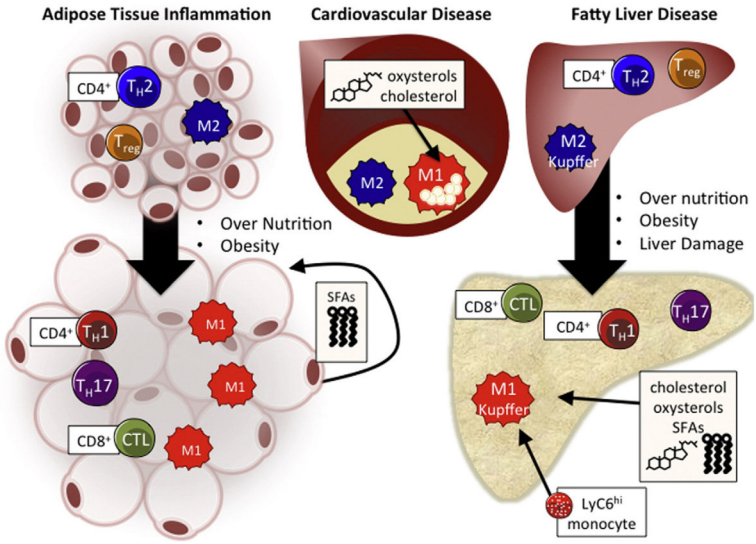

Fig. 1. Immune cell phenotypes in adipose tissue, arteries and liver during metabolic disease

In lean adipose tissue, $CD4^+$ lymphocytes and M2 macrophages express an antiinflammatory phenotype. During conditions of overnutrition or obesity, lipid mediators (SFA) are elevated and regulate the influx and activation of inflammatory macrophages (M1) and lymphocytes (Th1, CTL and Th17) in adipose tissue. In CVD, both M1 and M2 macrophages are present. In the arteries, macrophages infiltrate the arteries and engulf oxidized cholesterol, converting macrophages into foam cells. Similar to adipose tissue, the liver consists of antiinflammatory immune cells such as M2 associated Kupffer cells and $CD4^+$ lymphocytes (Th2 and Treg). In fatty liver disease, lipid levels are increased and lead to the recruitment of inflammatory monocytes ($Ly6C^{hi}$) that differentiate into M1 macrophages. Likewise, inflammatory Th1, CTL, and Th17 cells infiltrate the liver.

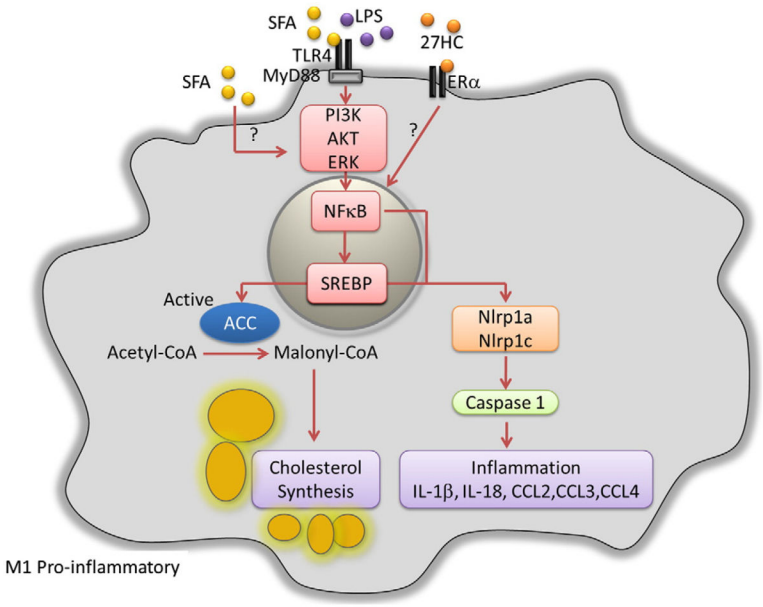

Fig. 2. SREBP activation is linked to a proinflammatory phenotype in macrophages

SFAs and LPS activate NFκB through TLR4-dependent and TLR4-independent pathways. Oxysterols (27HC) activate NFκB through estrogen-receptor-mediated signaling pathways. Activation of NFκB induces expression of inflammatory genes, driving the M1 phenotype. However, activation of NFκB also induces the expression of SREBP, promoting lipid synthesis and accumulation. SREBP regulates ACC expression, which drives cholesterol synthesis via the production of malonyl CoA.

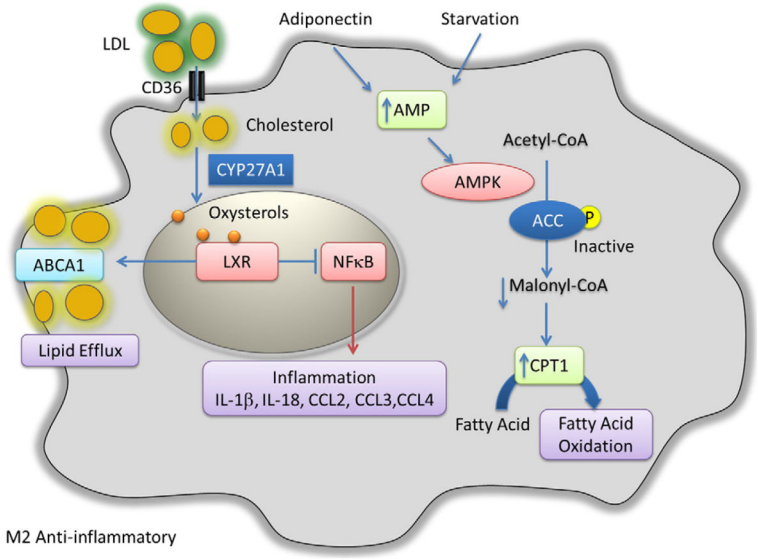

Fig. 3. Up-regulation of LXR and β-oxidation drives an antiinflammatory phenotype in macrophages

In macrophages, two lipid mediated pathways drive the antiinflammatory phenotype. (1) Cholesterol is taken by macrophages through the CD36 receptor. Cholesterol is converted into oxysterols by the enzyme CYP27A1. Oxysterols bind to LXR, leading to lipid efflux and cholesterol transport. Activation of LXR dampens inflammation by inhibiting the activity of NFκB. (2) AMP levels are elevated through metabolic factors such as adiponectin or starvation, leading to the activation of AMPK. AMPK inactivates ACC, leading to the reduction of malonyl CoA. Reduced malonyl CoA production increases CPT1 activity in mitochondria driving fatty acid oxidation.