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The mutual interplay of lipid metabolism and the cells of the immune system in relation to atherosclerosis

Atherosclerosis is a chronic inflammation in the arterial wall involving cells of the innate and adaptive immune system that is promoted by hyperlipidemia. In addition, the immune system can influence lipids and lipoprotein levels and cellular lipid homeostasis can influence the level and function of the immune cells. We will review the effects of manipulation of adaptive immune cells and immune cell products on lipids and lipoproteins, focusing mainly on studies performed in murine models of atherosclerosis. We also review how lipoproteins and cellular lipid levels, particularly cholesterol levels, influence the function of cells of the innate and adaptive immune systems. The overriding theme is that these interactions are driven by the need to provide the energy and membrane components for cell proliferation and migration, membrane expansion and other functions that are so important in the functioning of the immune cells.

Keywords: adaptive immune system • cellular lipid • cholesterol biosynthesis • cytokine • innate immune system • lipid efflux • lipid rafts • lipoprotein • oxysterol • plasma lipid

Atherosclerosis is the predominant underlying pathology at the core of much cardiovascular disease. It is a chronic inflammation of the large blood vessels involving cells of the innate and adaptive immune system [1]. The pathogenesis of atherosclerosis generally depends upon dyslipidemia, resulting in the retention of lipoproteins in the intima of arteries at risk, the local modification of the retained lipoproteins and the influx of monocytes which differentiate into macrophages that take up the modified lipoproteins thus forming the iconic cell type of early atherosclerosis, the foam cell. These foam cells as well as other cells in the vessel wall produce cytokines and chemokines with the consequent influx of additional monocytes as well as a variety of cells of the adaptive immune system, the most notable being subsets of T cells, which become activated locally. There are two major pathogenic thrusts that drive the development of atherosclerosis and its sequelae: dyslipidemia affecting each of the lipoprotein classes

on the one hand and inflammation, on the other, involving a number of different types of immune cells that 'instigate' the evolution of the chronic inflammation of the blood vessel wall. These two themes are not unrelated as we will attempt to explore in what follows. While we will review the interactive role of lipid metabolism and the immune system in general, it is in the context of atherosclerotic cardiovascular disease that these interactions have been most widely studied, given the front and center role of these two systems in the pathogenesis of this disorder. Hence much of the information on the interactions of lipid metabolism and the immune system is derived from the study of these systems.

The complexity of the atherosclerotic plaque has led to a vast field of preclinical studies. The most widely used models for the study of experimental atherosclerosis are genetically modified mice with increased levels of apoB-containing lipoproteins [2]. The apoE deficient (*ApoE*^{-/-}) mouse and the LDL receptor deficient (*Ldlr*^{-/-}) mouse are

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the most frequently used. ApoE is a major ligand for the clearance of atherogenic lipoproteins. It interacts with a variety of receptors of the LDL receptor family, including the LDL receptor itself, LDL receptor related protein-1 and VLDL receptor as well as cell surface proteoglycans. This apoprotein is found on chylomicron remnants, VLDL and HDL depending on the physiological context. *ApoE*^{-/-} mice are dyslipidemic when fed a standard chow diet, though a high fat western-type diet (WTD) containing 40% of calories as fat and supplementary cholesterol accentuates the dyslipidemia and accelerates atherogenesis. The accumulating lipoproteins are mostly chylomicron and VLDL remnants, with apoB48 as a major apoprotein. The LDL receptor is the receptor primarily responsible for atherogenic lipoprotein clearance. *Ldlr*^{-/-} mice are modestly hyperlipidemic on chow diet, but the feeding of a WTD is associated with a marked elevation of apoB-100 containing VLDL and LDL and the development of atherosclerosis. LDL receptor deficiency is often combined with overexpression of apoprotein B, either apoB100 or apoB48. The lipid composition of the VLDL differs in these two models, being enriched in cholesteryl esters in the *ApoE*^{-/-} model and enriched in triglycerides in the *Ldlr*^{-/-} model. Thus, although not to be discussed here in detail, the lipid components driving atherogenesis are not identical in these models.

In this review, we will not once again review the pathogenesis of atherosclerosis and the involvement therein of the many components of the immune system. The literature is replete with excellent recent reviews of these aspects [3,4]. We will instead focus on the mutual interaction of lipids and lipoproteins with cells of innate and adaptive immune system. We will address the following questions:

- What do we know about how the cells of the adaptive immune system influence the lipoprotein phenotype and function?
- What do we know about lipid homeostasis in cells of the immune system, particularly in response to proliferation?

These questions will be addressed in the background of our hypothesis that these interactions are driven by the need to provide the energy and membrane components for cell proliferation and migration, membrane expansion and additional trajectories that are so important in the functioning of both the innate and adaptive immune systems. Both immune systems are participants in a variety of acute inflammatory reactions and in the chronic inflammation associated with the evolution of the atherosclerotic plaque. As we will discuss, the immune cell often adopts cell-specific

strategies to manage its lipid metabolism in regulating its behavior in the immune response.

The immune system

The immune system has evolved to deal with pathogens so as to control or inactivate them to protect the host. The inflammatory response involves mobilizing cells and molecular mediators to the sites of microbial invasion or to sites of tissue injury. The first reaction is innate and exhibits general or limited specificity. It is often followed by the adaptive immune response, which is highly specific and often includes a memory component so that on a second encounter with the pathogen, there is a more immediate response. However, it should be kept in mind that there is a great deal of cross-talk between the two immune systems.

The innate immune system comprises a variety of cells, including neutrophils, macrophages and dendritic cells. These cells are attracted to the sites of invasion or injury by the production of chemoattractant molecules and expression of adhesion molecules on cell surfaces allowing these cells to migrate into the tissue where they contribute to the sequestration of the invader and in most cases ultimately its killing. The latter involves phagocytosis and fusion with endolysosomes, processes which depend on membrane elaboration/biogenesis. Within the endolysosomes, the ingested pathogens may be inactivated or killed by reactive oxygen species produced by oxidases along with a variety of hydrolytic enzymes. A variety of pathogens or pathogen-derived ligands are recognized by scavenger receptors, by complement receptors and by the Toll-like receptor (TLR) family of cell surface receptors. TLR recognizes pathogen-associated molecular patterns and signal within the cell for the production of cytokines and oxidative species. Other cells of the innate immune system include natural killer (NK) cells and mast cells that secrete killer molecules. An important function of the cells of the innate system, especially dendritic cells and macrophages, is the processing of protein and lipid antigens for presentation to the adaptive immune cells. The antigen presenting molecules are members of the major histocompatibility (MHC) family.

The responding cells of the adaptive immune system are B and T cells. Cell surface T-cell receptors (TCR), composed primarily of heterodimers of α and β chains, respond to the antigen presented in the context of MHC molecules on antigen-presenting cells (APCs). This is regarded as the first signal between the two interacting immune systems. The second signal is conveyed by costimulatory molecular pairs expressed on the APC and the T cell. Following recognition of specific antigens presented by MHC molecules by the

TCR and co-stimulation, the T cells undergo marked cell expansion. The T cells come in two major flavors; CD4⁺ cells (activated by MHC class II molecules) help to activate the cells of the immune system, and CD8⁺ cells that are generally cytotoxic. There are several subsets of CD4⁺ T cells; T helper (Th) 1 cells that secrete pro-inflammatory cytokines such as IFN- γ , IL-2 and TNF, Th2 cells that secrete IL-4 among other cytokines and T regulatory cells (Treg) that secrete IL-10 and TGF- β , anti-inflammatory cytokines. Recently, additional CD4⁺ subsets have been studied, including the Th17 cells that secrete IL-17. In addition to these canonical cytokines, the T cells produce a variety of other cytokines and chemokines through which they communicate with other elements of the immune system. The other major component of the adaptive immune system are B cells. The major B-cell subset, B-2 cells, secretes antibodies, largely members of the immunoglobulin G family.

There are additional members of the immune system that overlap both the innate and adaptive systems. This includes B-1 cells that secrete germ-line encoded antibodies, natural killer T (NKT) cells and $\gamma\delta$ T cells. The B-1 cells elaborate immunoglobulin M antibodies, including those targeted at oxidized lipids, such as is found in oxidized LDL and on apoptotic cells. The NKT cells recognize lipid antigens presented in the context of an MHC class I-like molecule called CD1. Recently, it has been shown that some subsets of $\gamma\delta$ T cells also recognize lipid antigens presented by CD1d [5].

The selective proliferation of cells of the immune system in response to activation, as well as their remodeling, requires energy and the raw materials, notably lipid including cholesterol, for the large extent of membrane expansion. We will review what little is known about the strategies employed by the immune cells to meet these demands.

Influence of the innate immune system on plasma lipids & lipoproteins

In response to an acute microbial infection, there is both a systemic response and a localized response at the site of the infection. These two responses are related in that the former is regulated by the production of the determining cytokines, particularly IL-1, TNF- α and IL-6, by the activated macrophages at the site of infection. Blood neutrophils and monocytes and resident macrophages migrate to the site of infection/injury, where they may recognize the microbe (via TLRs and scavenger receptors) and phagocytose the offending agent. Neutrophils have a very short half-life, may die (via apoptosis) at the site of inflammation and be cleared by phagocytosis (a process referred to as efferocytosis) by the local resident macrophages

or macrophages that have differentiated from the ingressing monocytes. This provides a significant amount of additional membrane components, especially lipids, in the phagocyte. We will discuss later in this review how the macrophage disposes of this lipid load. The systemic response is referred to as the acute phase response (APR) that comprises the production, mostly by the liver, of a panoply of APR proteins. Among the relevant proteins are C reactive protein (CRP) in humans, serum amyloid proteins (SAA) and complement proteins. The changes induced in lipid metabolism and lipoproteins in this model have been comprehensively reviewed by Khovidhunkit and colleagues [6]. An increase in plasma triglycerides and VLDL is observed, possibly related to an increase in fatty acid and triglyceride synthesis. Despite a reduction in lipoprotein lipase, this increase in plasma lipids can be viewed as a mechanism to furnish the energy-yielding substrates for tissue remodeling and healing associated with the resolution of the inflammation. Although the three prototypic cytokines are important in inducing the APR, it is not clear how important they may be in regulating the lipoprotein changes. At least in murine atherosclerosis models, interdiction of their signaling has little or quite modest effects on plasma lipoproteins. Increased complement 3B production facilitates the phagocytosis of microbes by functioning as an opsonin. Plasma SAA levels increase by as much as 1000-fold. SAA is an HDL-associated apoprotein and SAA-HDL is substantially remodeled and is dysfunctional, at least with respect to reverse cholesterol transport. Other HDL-associated proteins that exhibit changes during the APR are apoA-I, apoA-II, apoE and phospholipase A2. Although one of the functional outcomes of these changes is a reduction in the ability of HDL to promote reverse cholesterol transport, the full functional significance of these changes remains to be explored.

Influence of the adaptive immune system on plasma lipoproteins

One of the major functions of the monocyte/macrophage is to provide communication between the innate and adaptive immune systems in order to activate cells of the adaptive immune system, through their cytokine production, antigen presentation and expression of co-stimulatory molecules. In the next portion of this review, we focus on the impact of adaptive immune cells on plasma lipids and lipoproteins.

Our prior studies have indicated that *ApoE*^{-/-} mice on chow diet and *Ldlr*^{-/-} mice on WTD lacking both B and T cells due to deficiency of recombination activating genes have reduced plasma lipoproteins (Table 1), especially the apoB-containing lipoproteins [7]. It is

Table 1. Plasma cholesterol levels are reduced in the absence of B and T cells due to deficiency of recombination activating gene and increased in mice with increased levels of iNKT cells and deficiency of Treg cells.

Mouse model	Diet	Plasma cholesterol (mg/dl)	Ref.
<i>Ldlr</i> ^{-/-}	Chow	283	[7]
<i>Rag</i> ^{-/-} <i>Ldlr</i> ^{-/-}		192	
<i>Ldlr</i> ^{-/-}	WTD	720	[7]
<i>Rag</i> ^{-/-} <i>Ldlr</i> ^{-/-}		460	
<i>Ldlr</i> ^{-/-}	HFHSC	700	[8]
<i>Vα14tg.Ldlr</i> ^{-/-}		950	
<i>Ldlr</i> ^{-/-}	WTD	600	[9]
<i>Ldlr</i> ^{-/-} <i>FoxP3</i> ^{-/-}		1048	

HFHSC: High-fat, high-sucrose cholesterol-containing diet; WTD: Western-type diet.

not clear if this lipoprotein phenotype in these models is due to the loss of cell–cell interactions or soluble mediators. The observed reduction of plasma lipoproteins in these models may reflect a reduced requirement for plasma lipid components in the face of much lower replication of the various effector cells of their immune system. The mechanism by which this reduced requirement for energy and membrane components is sensed is very little explored. This immune-deficient model is complex, involving deficiencies of multiple subsets of B and T cells. As a result of cross-talk between immune cells, counter-regulatory networks could either accentuate or minimize the effects of specific immune cell deficiency. This needs to be borne in mind when evaluating effects of the apparent manipulation of individual T- or B-cell subsets.

Reduction of conventional B-2 cells, the major B-cell subtype, while influencing atherosclerosis, does not result in significant plasma lipid changes [10–12]. With these observations, it is not surprising that the focus has been on the various T-cell subsets.

Th1, Th2 & Th17 cells

The predominant effector T cell involved in acute inflammation and in promoting atherosclerosis is the Th1 cell, whose primary cytokine product is IFN-γ [3–4,13]. IFN-γ has previously been shown *in vitro* to reduce expression of scavenger receptor A, LDL receptor related protein-1 and lipoprotein lipase by macrophages. The exogenous administration of IFN-γ to *ApoE*^{-/-} mice fully backcrossed into C57BL/6 background led to a modest reduction of VLDL levels but increased atherosclerosis that was accompanied by an increase in lesional T-cell content. On the other hand, manipulation of IL-4 levels, which is produced by Th2 cells, has little impact on plasma lipids or lipoproteins and variable results on atherosclerosis [3–4,13]. It should

be borne in mind that these cytokines are produced by other cells of the immune system also. Th17 cells produce IL-17 and IL-22. In murine models, IL-17 does not appear to influence plasma lipids and has variable effects on atherosclerosis [14–17]. *In vitro*, IL-17 has been shown promote the expression of pro-inflammatory cytokines by endothelial cells, and these cytokines in turn promote the uptake of oxidized lipids by macrophages and promote foam cell formation [18]. IL-22 is also produced by Th22 cells in response to the Th1 cytokines IL-6 and TNF-α and the RAGE ligand S100/calgranulin. A recent study has shown that IL-22 promotes lipid accumulation in macrophages and this is associated with a significant decrease in the expression of the ATP-binding cassette (ABC) G1 gene [19].

Natural killer T cells

NKT cells merit particular attention in the discussion of lipoprotein homeostasis and immune cells as they recognize lipid antigen presented by CD1 molecules [20]. These antigens may be exogenous (e.g., microbes) or endogenous (e.g., plasma or cellular lipids). The precise nature of the endogenous antigens remains to be clarified. NKT cells have characteristics that bridge the innate and adaptive immune systems and are activated to produce both Th1 cytokines (e.g., IFN-γ) and Th2 cytokines (e.g., IL-4). There are two major NKT-cell subclasses. The predominant invariant NKT (iNKT) cell or type I NKT cell expresses the relatively invariant TCR-α chain Vα14-Jα18 in mice and Vα24-Jα18 in humans. The TCRs in the less abundant type II NKT cell are more diverse. Despite the fact that iNKT cells are highly enriched in the liver, where a good deal of lipid and lipoprotein regulation occurs, their reported impact on these parameters is relatively modest and quite variable between studies. An increase in plasma triglyceride was noted in mice lacking iNKT only (*Ja18*^{-/-} mice) or both

types of NKT cells (*Cd1d*^{-/-} mice) when fed a standard low fat diet by one group [21], but not others [22–27]. These studies used animals expressing the LDL receptor and apoE and thus the animals were only moderately hyperlipidemic. A number of laboratories studying NKT-cell influence on atherosclerosis in *ApoE*^{-/-} mice have also not seen any plasma lipid changes as a function of NKT-cell status [28]. In our laboratory, we have studied *Ldlr*^{-/-} mice deficient in NKT cells and mice with increased levels of iNKT cells due to expression of the Vα14 transgene (*Vα14tg*). Two diets have been employed; the WTD and a high-fat, high-sucrose, cholesterol-containing diet (HFHSC) that differ not only in energy substrates but also in the source of fat – milk fat and lard, respectively. In WTD-fed male animals, we observed no differences in plasma lipids and lipoproteins in *Vα14tg.Ldlr*^{-/-} and *Ja18*^{-/-}*Ldlr*^{-/-} mice compared with *Ldlr*^{-/-} mice. However, female *Ja18*^{-/-}*Ldlr*^{-/-} mice had elevated total cholesterol levels in the plasma (unpublished observations). In animals fed the HFHSC diet, the *Vα14tg.Ldlr*^{-/-} mice (**Table 1**) [8] and *Ja18*^{-/-}*Ldlr*^{-/-} mice (unpublished observations) had higher plasma VLDL and LDL compared with *Ldlr*^{-/-} controls. Interestingly, the *Cd1d*^{-/-}*Ldlr*^{-/-} mice had the highest level of these lipoproteins. These results are apparently paradoxical and suggest that the responses are quite complex, possibly involving unidentified mediator cells or molecules. Clearly much further work is required to lead to a mechanistic understanding of these plasma lipid excursions mediated by NKT cells. Given that the studies with the HFHSC diet were performed during the course of obesity investigations, the recently elucidated interaction between obesity and the gut microbiome [29], as well as the ability of NKT cells to be activated by microbial antigens, the interaction of the NKT-cell complement and the microbiome should be considered. The possible involvement of the microbiome may account for at least some of the variability of results from different laboratories.

Regulatory T cells

A recent report by Klingenberg and colleagues [9] notes that selective depletion of Treg cells in *Ldlr*^{-/-} mice leads to increased aortic root atherosclerosis and increased plasma cholesterol levels (**Table 1**) due to increased levels of VLDL/chylomicron remnants levels. This appears to be associated with reduced clearance of these lipoproteins, possibly related to a reduction in hepatic *sortilin-1* expression. Sortilin-1 is a recently identified hepatic protein that promotes the trafficking of apoB-containing lipoproteins in the Golgi or bound to the cell surface to lysosomes for degradation. Expression of hepatic genes for lipid metabolizing proteins is also altered in the Treg depleted environment, with increased expression of lipoprotein

lipase, hepatic lipase and phospholipid transfer protein as well as the VLDL receptor. This study eliminated FoxP3⁺ Treg cells. But it should be borne in mind that Tregs are not a homogeneous set of cells with the possibility of different functions by subsets of these cells [30].

The molecular basis for the regulation of lipoprotein metabolism in hepatocytes by Tregs has yet to be established. At a first approximation, the absence of the major suppressive cytokines produced by Tregs, namely, TGF-β and IL-10, may be mediating these effects. While recognizing that other cell types also produce these cytokines, the effect of interrupting signaling by these cytokines has been explored (reviewed in [13]). Global knockout of TGF-β cannot be investigated as its absence is incompatible with survival. Abrogation of TGF-β signaling in T cells by expression of a dominant-negative TGF-β receptor exhibits no change in plasma lipids in the *Ldlr*^{-/-} model. In the *ApoE*^{-/-} model, however, a reduction in total plasma cholesterol and in VLDL/chylomicron remnants was noted despite an increment in atherosclerosis. Similar lipid changes were seen with interference with receptor signaling in dendritic cells in *ApoE*^{-/-} mice [31]. Interestingly, in both studies in *ApoE*^{-/-} mice, abrogation of TGF-β signaling in the immune cells had no effect on plasma triglycerides. TGF-β signaling involves activating SMAD mediators, including SMAD 2, 3 and 6, while SMAD 7 is an inhibitor of TGF-β signaling. Thus removal of SMAD 7 should augment TGF-β activity. Interestingly, the transplantation of bone marrow selectively lacking *Smad7* into *Ldlr*^{-/-} mice results in a substantial increment in plasma triglyceride affecting mostly VLDL/chylomicron remnants in high-fat diet-fed animals [32]. The other major cytokine product of Tregs is IL-10. Upon IL-10 overexpression in T cells in wild-type mice and upon transplant of bone marrow from the IL-10 transgenic mice into *Ldlr*^{-/-} mice, only modest changes in lipoprotein levels were observed [13]. A slight reduction in HDL levels was observed in global *Il10*^{-/-} mice, but not when bone marrow from *Il10*^{-/-} mice was transplanted into *Ldlr*^{-/-} mice. On the other hand, *Il10*^{-/-}*ApoE*^{-/-} mice, while showing no change in total plasma cholesterol or triglyceride, did manifest a decline in VLDL levels and an increase in LDL. The fact that TGF-β and IL-10 are secreted by several cell types and responses could affect different cells suggests that these cytokine and cellular interactions are quite complex, especially when differences between *ApoE*^{-/-} and *Ldlr*^{-/-} models are taken into account. This axis of regulation requires much more study.

Co-stimulatory effects

As mentioned above, the full activation of T cells requires the participation of co-stimulatory molecules

involving ligands and receptors expressed on the T cells and APCs. There are several families of costimulatory molecules, with the best characterized being the CD28 superfamily and the TNF receptor related family. A variety of studies have manipulated costimulation via B7/CD28, ICOS/ICOSL, O $\times$ 40/O $\times$ 40L, CD137 (IBB)/CD137L, CD30/CD30L, CD40-TRAF6/CD40L and PD1/PDL in either the *Apoe*^{-/-} model or the *Ldlr*^{-/-} model. In none of these cases has a change in plasma lipid levels been reported [33–39]. On the other hand, the LIGHT/lymphotoxin co-stimulatory family, members of the TNFR family, do have an influence on plasma lipids in the *Ldlr*^{-/-} mice. The ligands LIGHT, lymphotoxin α (comprising a homotrimer of lymphotoxin (Lt) α subunits) and lymphotoxin β (a heterotrimer of one Lt α and two Lt β subunits) are expressed mainly in T cells. LIGHT and lymphotoxin β are cell surface membrane bound, while lymphotoxin α is secreted. Lymphotoxin α signals via TNFRs, lymphotoxin β signals predominantly via the lymphotoxin β receptor (LT β R), while LIGHT signals through both the LT β R and herpes virus entry mediator (HVEM). The receptors are more widely expressed than are the ligands, especially LT β R which is expressed on epithelial cells including hepatocytes in addition to immune cells. The overexpression of LIGHT in T cells leads to a profound downregulation of hepatic lipase expression in the liver via signaling through the LT β R [40]. In both the presence and absence of the LDL receptor, the transgene-mediated reduction of hepatic lipase results in the accumulation of an enlarged HDL, designated HDL₁ [A REARDON & GS GETZ, UNPUBLISHED DATA]. This lipoprotein has apoE as its major protein with no apoB and very little apoA-I, the characteristic protein of HDL. We presume that

this lipoprotein depends on hepatic lipase for its metabolism or uptake. When LIGHT is expressed in mice via an adenovirus, primarily targeting hepatocytes, hepatic lipase is still downregulated, indicating that T cells are not obligatory for this regulation [41]. The knockout of *Light* does not increase hepatic lipase expression, but in the *Ldlr*^{-/-} background when *Light*-deficient mice are fed the WTD for 12 weeks we see a notable reduction in the steady-state level of HDL cholesterol as well as apoB-containing lipoproteins (Table 2). This reduction in plasma lipoproteins is even more obvious with the deficiency of the LIGHT receptor HVEM in the *Ldlr*^{-/-} background. We suspect that this is attributable to a difference in lipoprotein catabolism, as in preliminary studies we find no difference between *Ldlr*^{-/-} mice and *Hvem*^{-/-} *Ldlr*^{-/-} for VLDL production and lipid absorption. *Light* and *Hvem* deficiency are not associated with a reduction of lipoprotein levels until after 6 weeks of WTD feeding. Plasma lipid levels increase progressively with the continuing feeding of the *Ldlr*^{-/-} mice with WTD. This does not occur in both *Light* and *Hvem*-deficient mice. Rather plasma lipid levels plateau after the initial 6 weeks of diet. This data suggest that this ligand receptor-axis interacts with proteins in the liver that change as a function of time during dietary lipid loading.

Lymphotoxin ligand–receptor interactions also affect lipoprotein metabolism. Since lymphotoxin α and lymphotoxin β share the Lt α subunit, the elimination of the Lt α subunit impacts both forms of lymphotoxin. We have crossed global *Lta*^{-/-} mice and mice with *Ltb* knocked out selectively in T cells with *Ldlr*^{-/-} mice. Both of these animals exhibit a reduction of total plasma cholesterol with 12 but not 6 weeks of

Table 2. Plasma lipid and lipoprotein changes upon alteration in the expression of the LIGHT/ lymphotoxin co-stimulatory family in female <i>Ldlr</i> ^{-/-} mice fed a western-type diet for 12 weeks. All differences are relative to control <i>Ldlr</i> ^{-/-} mice.			
LIGHT/Lymphotoxin family models	Site of expression/ deficiency	Plasma lipid effects	Lipoprotein effects
Transgene			
LIGHT	T cell	↑	↑ HDL ₁
Deficiency			
LIGHT	Global	↓	↓ VLDL, LDL, HDL
Lt α	Global	↓	↓ VLDL, LDL
Lt β	T cell	↓	↓ VLDL, LDL
HVEM	Global	↓	↓ VLDL, LDL, HDL
LT β R	Global	–	
HDL: High-density lipoprotein; HVEM: Herpes virus entry mediator; LDL: Low-density lipoprotein; <i>Ldlr</i> ^{-/-} : LDL receptor deficient; Lt: Lymphotoxin; LT β R: Lymphotoxin β receptor; VLDL: Very low density lipoprotein. Data from [A REARDON & GS GETZ, UNPUBLISHED DATA].			

WTD feeding. VLDL cholesterol and LDL cholesterol were both reduced. Although lymphotoxin β interacts primarily with the LT β R, global removal of this receptor does not have similar effect on plasma lipids as the ligand knockout. This may be accounted for by the expression of lymphotoxin β by immune cells other than T cells. However, plasma triglycerides are reduced in the LT β R knockout mice at 12 weeks of diet feeding. The results of manipulating these ligands and their cognate receptors are discussed in the hope of providing some insight for the understanding of the low plasma lipids we have reported in mice lacking both T and B cells. While these ligands and receptors expressed in cells of the adaptive immune system may contribute to this phenotype, they cannot on their own fully account for the immune deficiency finding. They may interact with other undetermined mediators to fully account for the phenotype. For example, the difference between *Ldlr*^{-/-} and *Rag*^{-/-}*Ldlr*^{-/-} mice is detectable in chow-fed animals while the differences seen in the *Lighr*^{-/-}, *LTa*^{-/-} or *LTb*^{-/-} mice in the absence of the *Ldlr* are only seen after 12 weeks of feeding the WTD. Few of the studies of other co-stimulatory molecules have examined plasma lipids as a function of diet duration. The complex response of plasma lipids to LIGHT/lymphotoxin and their receptors merits further study.

Lipid homeostasis in the cells of the immune system

Cholesterol is an essential lipid required for membrane biogenesis, so that it is not surprising that the control of its level is critically regulated. The seminal observation by Brown and Goldstein of the robust uptake of lipoprotein lipids by macrophages lacking the LDL receptor directed study to the participation of scavenger receptors in this process. In this section, we will review aspects of the lipid homeostasis in macrophages and various lymphocyte populations that are major participants in atherogenesis.

Macrophages

There are two major subclasses of monocytes in the blood; patrolling Ly6C^{lo} monocytes and the more inflammatory Ly6C^{hi} cells [42]. Ly6C^{hi} cells are the major subclass to infiltrate the evolving atherosclerotic plaque, where they differentiate into macrophages and become foam cells. Signals within atherosclerotic plaques polarize the macrophages into different phenotypes [43,44]. The M1-like macrophages are the predominant cell in progressing atherosclerotic plaques and secrete pro-inflammatory cytokines. The alternatively activated M2-like macrophages are reparative and are enriched in plaques undergoing regression. The selective lipid

regulatory circuits in these two macrophage subsets are yet to be categorically explored. In contrast to the long held view that accumulation of macrophages in the lesion is mainly the result of continuing recruitment of blood monocytes, it has recently been shown that local proliferation is a major contributor to this accumulation also [45]. The extent to which cholesterol and lipid homeostasis play a controlling role in this proliferation, as is the case for the monocyte precursors in the bone marrow (see Hematopoiesis section below), has yet to be fully explored.

In the presence of hyperlipidemia, macrophages are rapidly converted to foam cells in the arterial wall. The lipid load of these cells is a function of the equilibrium between scavenger receptor mediated uptake of locally modified lipoproteins and lipid efflux, either of which can predominate in a variety of pathophysiological contexts. Many studies have explored the mechanisms involved in lipid uptake and efflux from macrophages [44,46]. The lipid that accumulates in the foam cell initiates important physiological processes. The free cholesterol released from the endocytosed modified lipoproteins passages from the lysosome to the endoplasmic reticulum, where it is either re-esterified to cholesteryl ester by the enzyme acylCoA: cholesterol acyltransferase (ACAT) or becomes a part of a sterol regulatory pool. Changes in the regulatory pool modulate expression of genes associated with *de novo* lipogenesis and uptake of LDL into cells via influencing the trafficking of sterol response element binding protein (SREBP) to the nucleus, as has been elegantly elucidated in studies from the Brown and Goldstein laboratory [47]. In addition, oxygenated-derivatives of cholesterol serve as ligands for the nuclear receptor liver X receptor (LXR) which by upregulating the synthesis of sterol efflux ABC transporters promote the export of excess cellular cholesterol as well as the transrepression of some inflammatory pathways [48]. The importance of cholesterol as a regulator of the synthesis of a variety of proteins is clearly depicted by the macrophage cholesterol responsive network identified by the comparison of proteins secreted from peritoneal macrophages of *Ldlr*^{-/-} animals fed chow or WTD [49]. Included among the 46 proteins found to be differentially regulated with cholesterol loading *in vivo* are proteins involved in lipid metabolism, proteolysis and complement activation. Interestingly and unexplained, is the observation that apoE, which is a network 'hub,' was downregulated in the macrophages loaded with lipid *in vivo*, but was notably upregulated when macrophages in culture were loaded with acetylated LDL [49,50].

So how may these major changes in macrophage phenotype be influenced by cholesterol load? Activation of LXR by oxysterols or intermediates in

the cholesterol biosynthetic pathway regulates the expression of a number of genes involved in cholesterol and lipid metabolism (Figure 1). The activation of LXR could be regarded as a mechanism to integrate/orchestrate the complex response of the macrophage to a lipid load involving anti-inflammatory or lipid unloading effects [48]. Elements of this response are reviewed below. Spann and colleagues performed a very careful lipidomic analysis of peritoneal macrophages of wild-type and *Ldlr*^{-/-} mice lipid loaded *in vivo* by the feeding of a WTD compared with cells obtained from animals maintained on standard low fat chow [51]. Desmosterol, a late intermediate in cholesterol biosynthesis, was the endogenous LXR ligand that accumulated to the largest extent in the cholesterol-loaded cells. While overall sterol biosynthesis is downregulated due to the retention of SREBP2 in the endoplasmic reticulum leading to a significant reduction in the expression of the rate-limiting enzyme in cholesterol biosynthesis HMGCoA reductase, desmosterol accumulates in the cholesterol-loaded macrophages as a result of an even more profound reduction of 24-dehydrocholesterol reductase expression, the enzyme that converts desmosterol to cholesterol. This fine tuning of the pathway accounts for this pattern of sterol accumulation. Desmosterol also accumulates in the foam cells of atheromatous plaques. Indeed, the accumulation of oxysterols, often assumed to be important endogenous ligands for LXR, was modest in the *in vivo* lipid-loaded macrophage. Their involvement as major LXR ligands in the cholesterol-loaded macrophages was essentially ruled out by the lack of an effect of the genetic removal of the hydroxylases responsible for oxysterol generation on LXR target genes. This does not exclude the participation of the oxysterols as LXR ligands in other circumstances, as they have higher affinity for LXR than does desmosterol. ABCA1 and ABCG1, two important LXR target genes, were increased by desmosterol treatment.

Figure 1. Oxysterols and cholesterol biosynthetic intermediates, such as desmosterol, influence a variety of functions in immune cells. Liver X receptor has a major role in the effects on lipid efflux and proliferation, and anti-inflammatory functions, although some of liver X receptor's anti-inflammatory function is independent of oxysterols.

The induction of these transporters will promote cholesterol efflux in the presence of apoprotein and HDL acceptors. Thus, in the face of a cholesterol overload a complex regulatory network is induced in macrophages to attempt to maintain cellular cholesterol homeostasis. It is not yet clear that this regulatory network also applies in other cell types, for example, hepatocytes loaded with sterols.

In contrast to loading of macrophages with modified LDL in culture, the *in vivo* cholesterol-loaded macrophages were anti-inflammatory as manifested by reduced expression of the cytokine IL-1 β and chemokines CXCL9 and CXCL10 [51]. This response was not seen in cells lacking LXR. The foam cells in lesions are diverse, some of which are anti-inflammatory [52]. Much of the cholesterol derived from the uptake of lipoproteins is 'inactivated' by esterification by ACAT, forming the lipid droplets of the foam cells. Inhibition or inactivation of this enzyme results in the accumulation of free cholesterol in the endoplasmic reticulum, which induces the unfolded protein response and ultimately the initiation of apoptosis [53]. The fatty acids employed for the esterification of cholesterol may be derived from the hydrolysis of the glycerides present in the incoming lipoproteins. However these fatty acids can also be further modified intracellularly by desaturation. The predominant acyl groups on the stored sterol esters are mono-unsaturated palmitic and stearic acid, arising from the action of stearyl CoA dehydrogenase. This enzyme is also upregulated by the activation of SREBP1c, an LXR target gene. The initiation of the macrophage cholesterol regulated network can also occur upon the uptake of apoptotic cells. This adds membrane-derived cholesterol to the phagocyte and, in an LXR-dependent pathway, upregulates the MerTK receptor that promotes further uptake of apoptotic cells [48,54]. This efferocytosis of apoptotic cells helps to reduce the necrotic core in the lesions and thus promotes stable plaques [55]. The activation of LXR following the uptake of apoptotic cells also leads to suppression of inflammatory pathways, thus likely repressing autoimmune responses. This latter response is however independent of apoE or ABC transporters, important LXR target genes involved in regulating cellular cholesterol homeostasis. In the resolution of an acute inflammation many of the neutrophils will die by apoptosis and be efferocytosed by macrophages. This will occur in the context of high IL-6 levels. Macrophages respond to IL-6 by upregulating ABCA1 expression via Jak-2/Stat-3 signaling thus increasing the capacity of the macrophage to efflux the cholesterol derived from the phagocytosed apoptotic cells [56] so that it can be transported to the liver for conversion to bile acids. MerTK is also upregulated, thus facilitating the continuing efferocytosis of aged neutrophils [57].

Even though oxysterols may not be the predominant endogenous ligands for LXR in the cholesterol overloaded macrophages, they nevertheless do participate in immune cell cross-talk. Some of these actions have recently been reviewed [58]. These include promotion of inflammasome activation by SREBP1a [59] and antiviral activity of 25-hydroxycholesterol [60]. The morphological differentiation of secondary lymphoid organs is also partially dependent on oxysterol signaling. An oxysterol gradient plays a role in the migration of B cells and a subset of dendritic cells to specific regions within the spleen during a humoral immune response. This positions these cells optimally for the recognition of exogenous antigens and is necessary for an appropriate antibody response. The sterol involved here is 7α , 25-dihydroxycholesterol generated by the enzymes 25-hydroxylase and CYP7B1 in the lymphoid stromal cells. This oxysterol is a ligand for G-protein-coupled receptor EB12 (GRP183). GRP183 expression on B cells is required for the B-cell segregation to the B/T zone and to inter and outer follicular regions during different phases of the immune response [61–63]. GRP183 expression on the CD4⁺ dendritic cell subset is required for their migration to marginal zone bridging channels [64]. 7α , 25-dihydroxycholesterol is inactivated by HSD3B7, a steroid oxidoreductase. The differential distribution of the biosynthetic and degradation enzymes in the spleen creates a gradient of the GRP183 ligand. The migration of the immune cells to the marginal zone, mediated in part by this oxysterol gradient, results in lymphotoxin β on B cells initiating signaling in antigen-presenting CD4⁺ dendritic cells in the marginal zone, following which the latter migrate into the T zone of the follicle in an LT β R- and CCR7-dependent fashion. *Ccr7* is a sterol responsive gene that participates in the regression-dependent emigration of foam cells from atherosclerotic plaques [65]. Whether the CCR7-dependent migration of dendritic cells into the T zone of the splenic follicle is sterol regulated is not clear.

One of the mechanisms for the anti-inflammatory action of LXR agonism is dependent on the activity of the LXR target ABCA1, which plays a role in the redistribution of free cholesterol from lipid raft domains to nonraft domains of the plasma membrane [66]. Lipid rafts are plasma membrane microdomains enriched in free cholesterol and sphingolipids and are platforms for the sequestration of signaling receptors. Thus macrophages deficient in ABCA1 are hypersensitive to TLR2, 4, and 7 in a MyD88-dependent pathway. This hypersensitivity can be reversed by removal of the free cholesterol from the lipid rafts with cyclodextrin. Rafts also have a higher ratio of lysolecithin to lecithin. As a result, lysophosphatidylcholine acyltransferase

(Lpcat), which converts the lysophosphatidylcholine to phosphatidylcholine usually with an unsaturated fatty acyl chain, can reverse the hypersensitivity to TLR4 signaling [67]. In fact, *Lpcat3* is a target of LXR and is responsible for the remodeling of phospholipids in macrophages resulting in a reduction in endoplasmic reticulum stress [68]. Additional targets of LXR include other ABC transporters, ABCG1, ABCG5 and ABCG8. With respect to cholesterol efflux, ABCA1 and ABCG1 have received most attention. Both transporters are highly expressed in lipid-loaded macrophages and are generally differentiated by the acceptors for the effluxed cholesterol; lipid-poor apoproteins, particularly apoA-I, and HDL, respectively. However recent work has suggested that these transporters differ in another important respect. ABCA1 is a cell surface transporter that binds apoA-I [69]. ABCG1, on the other hand, is predominantly intracellular, being found particularly in endosomal and recycling membranes [70]. The action of this transporter seems to be to extract free cholesterol from the endoplasmic reticulum, thus reducing stress in this organelle as well as reducing the regulatory pool of free cholesterol leading to the activation of SREBP precursor processing and increased expression of SREBP target genes. In as much as the transporter is in recycling endosomes, it may dynamically associate with the plasma membrane to hand off its cholesterol to the HDL acceptor even with the steady-state concentration of this transporter at the plasma membrane being quite low. This trajectory has yet to be clearly established. As suggested, the redistribution of cholesterol between lipid raft domains and other domains of the plasma membrane may account for some of the anti-inflammatory action of LXR. On the other hand, LXR is anti-inflammatory even in the absence of the ABC transporters [71]. The disruption of the corepressor NCoR-LXR complexes leads to derepression of LXR and results in the local macrophage biogenesis of palmitoleic acid and 3 polyunsaturated fatty acids, which bind to GPR120, resulting in a reduction in TLR- and TNF-dependent inflammation [72]. In addition, sumoylation of ligated LXR targets it to the promoters of NF- κ B target genes and prevents signal-dependent release of the co-repressor from the promoters leading to a reduction in pro-inflammatory gene expression [73].

Hematopoiesis

Recent work has shown that cholesterol homeostasis and redistribution of free cholesterol from lipid rafts also plays a very significant role in the proliferation of myeloid precursor cells in the bone marrow. The association of blood monocytosis with atherosclerosis in a variety of models and circumstances is a recently

appreciated mechanism linking hyperlipidemia and cholesterol efflux with atherogenesis [74]. The mechanisms associated with these associations were initially studied by Tall and collaborators. They showed that hematopoietic stem multipotent progenitor cells (HSPC, Lin⁻ Sca⁺ cKit⁺ cells), granulocyte monocyte progenitor (GMP) cells and common myeloid progenitor cells, but not common lymphoid progenitor (CLP), proliferate to a greater extent in the bone marrow of animals globally lacking ABCA1 and ABCG1 resulting in blood monocytosis and granulocytosis [75]. These effects were suppressed by the infusion of HDL or the *in vivo* overexpression of apoA-I by transgenesis. This presumably reflects the existence of other pathways of cholesterol efflux other than those mediated by the two ABC transporters. The response of these lineages to cholesterol overload, consequent on ABC transporter deficiency, was to increase lipid raft formation and expression of the common β subunit of the receptors for IL-3 and GM-CSF, thus rendering the cells more sensitive to the proliferation stimulated by the growth factors (Figure 2). A role for apoE in regulating expansion and proliferation of HSPC was also established. Monocytosis is more obvious in *ApoE*^{-/-} mice than *Ldlr*^{-/-} mice fed WTD. This is not seen in *ApoA1*^{-/-} mice, nor did the absence of apoA-I in *ApoE*^{-/-} mice further enhance the monocytosis observed in *ApoE*^{-/-} mice [76]. ApoE is bound to heparan sulfate proteoglycans of the HSPC cell surface, impeding their proliferation in a cell autonomous fashion and in an ABC transporter-dependent mechanism. This strongly suggests that the ABC transporter mediated removal of cholesterol from the lipid-rich domains of the HSPC cells is enhanced by cell surface apoE.

Figure 2. Decreased lipid efflux due to deficiency of ABCA1 and ABCG1 in HSPC in the bone marrow leads to increased number of lipid rafts and expression of the common β subunit of the receptor for IL-3 & GM-CSF, rendering the progenitor cells more responsive to the growth factors. This leads to monocytosis and neutrophilia in the blood. ApoE also has a role in the proliferation of HSPC. HSPC: Hematopoietic stem multipotent progenitor cell.

The selective knockout of the two ABC transporters in macrophages and not HSPC highlights the role of the spleen, a secondary lymphoid organ, in facilitating hematopoiesis [77]. In this model, monocytosis and neutrophilia is observed without HSPC proliferation. Increased expression of *M-csf* and *G-csf* in the spleen is likely enhancing monocyte and GMP proliferation in the bone marrow. At least part of the mechanism involves increased secretion of IL-23 from splenic macrophages and dendritic cells deficient in ABCA1 and ABCG1, which in turn promotes increased IL-17 production by Th17 cells with a consequent increment in G-CSF expression [78]. IL-3- and G-CSF-mediated splenic extra medullary hematopoiesis plays a role in the provision of monocytes that infiltrate atherosclerotic lesions [79].

Lymphocytes

In response to antigen stimulation, lymphocytes of the adaptive immune system undergo profound proliferation, requiring the provision of lipids for membrane biogenesis. More than 25 years ago, Cuthbert and Lipsky showed that the provision of lipids from LDL or apoE-containing lipoproteins via the LDL receptor were required for mitogen-stimulated proliferation of human blood derived T cells [80]. The possibility that LDL might have carried other growth factors to these cells could not be excluded. Consistent with the need for additional lipids, the stimulation of lymphocyte proliferation with anti-CD3 resulted in the upregulation of HMGCoA reductase [81].

Recently the involvement of lipids in the proliferative responses of lymphocytes has been more extensively investigated. The mechanisms involved are distinct from those just outlined for monocytes and neutrophils. It is notable that the CLP in the bone marrow that gives rise to lymphocytes is not affected by the deficiency of *Abca1* and *Abcg1* [75]. This is perhaps not surprising given the variety of antigens and T-cell subsets involved in the adaptive immune response that might require selective proliferative mechanisms. This is borne out by cholesterol homeostatic mechanisms. *Ldlr*^{-/-}*ApoA1*^{-/-} double-knockout mice exhibited notable lymph node enrichment in cholesterol and immune cell hyperplasia with accompanying signs of autoimmunity when fed a high fat, high cholesterol diet [82]. These effects were attenuated by the adenoviral-mediated expression of apoA-I or subcutaneous injection of lipid-free apoA-I [82,83] suggesting that cholesterol homeostasis in lymphocytes might be regulating the hyperplasia.

The intravenous injection of squalene, a cholesterol precursor, results in cholesterol enrichment of cell membranes of several resting T-cell subsets

[84]. Stimulation of these cholesterol enriched CD4⁺ T cells with anti-CD3 or activated APCs showed increased polarization toward inflammatory Th1-type responses as evidenced by increased secretion of IL-2 and IFN- γ and decreased secretion of IL-4. Although similarly enriched with lipid, the Treg cells did not manifest increased suppressor activity upon activation. Cholesterol accumulation in T cells in *Abcg1*^{-/-} animals is associated with enhanced proliferation of thymocytes and peripheral lymphocytes [85]. The enrichment of the membranes with cholesterol appears to enhance TCR signaling via increased phosphorylation of ZAP 70 and ERK1/2. Indeed, inhibition of the phosphorylation of ERK1/2 attenuates the hyperproliferation upon activation of the TCR. These data suggest that the accumulation of cholesterol as a result of impaired efflux may 'prime' cells for proliferation.

In addition to impaired cholesterol efflux, enhanced lipid biosynthesis can also provide additional lipids and sterols required by activated lymphocytes. Following clonal stimulation of primary T cells, pathway analysis revealed a major change in lipid metabolizing gene clusters in effector T cells. Expression of SREBP target genes were increased, while LXR target genes, including *Abcg1* and *Abca1*, were decreased [86]. SREBP-mediated expression of genes in lipid and sterol biosynthesis in activated CD8⁺ T cells is essential for the cells to blast and to proliferate and survive, thus providing lipids for new membrane synthesis [87]. The repression of LXR target genes appears to be related to the regulation of endogenous LXR ligand availability due to the rapid induction of the oxysterol sulfur transferase SULT2B1, which inactivates oxysterols as LXR ligands [86]. The importance of LXR signaling regulating lymphocyte proliferation was demonstrated by the reduced proliferation of T cells treated with synthetic LXR ligands and enhanced proliferation by T cells lacking *Lxr β* . LXR-mediated reduction of lymphocyte proliferation was via an ABCG1-dependent alteration in intracellular sterol trafficking, likely leading to reduced cellular cholesterol. Thus a complex network of gene transcription accompanies effector T-cell activation and expansion. Together SREBP and LXR, as well as perhaps other transcription factors that promote expression of genes involved in lipid metabolism, ensure that sufficient cellular cholesterol and lipid is available to support effector T-cell proliferation in response to antigenic stimulation. In addition to sterol biosynthesis and efflux, uptake of lipoproteins also plays a role in cellular cholesterol homeostasis, with uptake in T cells mediated by SRBI [88]. Interestingly, the proliferation of memory cells does not appear to involve these same mechanisms.

However not all subsets of lymphocytes hyperproliferate in the absence of *Abcg1*. iNKT cells in liver and thymus are decreased in *Abcg1*^{-/-} mice as a result of both decreased proliferation and decreased maturation at early stages of development [89]. Cholesteryl esters do not accumulate in iNKT cells perhaps due to a compensating increase in *Abca1* in the absence of *Abcg1*, and there was a reduction in lipid rafts in these cells. Functionally, these iNKT cells exhibit a cytokine preference for secretion of IFN- γ over IL-4.

The differential response of the various T-cell subsets to alterations in cellular cholesterol is further highlighted by a recent examination of γ/δ T cells [90]. This T-cell subset has a higher cholesterol content that is associated with increased lipid raft content and elevated expression of several genes regulating cellular sterol homeostasis compared with CD4⁺ T cells. The authors suggested that these cholesterol enriched γ/δ T cells are 'more activated' than CD4⁺ T cells resulting in faster proliferative response to stimulation. Removal of cellular cholesterol reduced lipid rafts and their state of activation.

Conclusion

A characteristic of both the innate and adaptive immune systems is the selective expansion of cells as the immune response evolves. Energy often provided by lipids, and membrane lipid components are essential for the cell expansion and membrane remodeling. Cell signaling is also implicated by the redistribution of lipids to membrane subdomains. It is becoming clear that different strategies are adopted by each of the cells of the immune system to meet these needs. We have reviewed what is currently known about these issues. The mechanisms by which the immune systems regulate their energy supply and plasma lipoproteins in particular are poorly understood.

Future perspective

The molecular mediators of the interactions between lipids and immune cells and their progenitor cells are yet to be clarified. As we learn more about the mechanisms by which immune cells modulate lipid metabolism and how lipids modulate the proliferation or functional properties of immune cells, important therapeutic targets for manipulation of a dysfunctional immune system, not only in relation to atherosclerosis, but many other chronic inflammatory disorders may arise. However in seeking these therapeutic targets, the differential behavior of the elements of the immune system has to be born in mind. In addition, undoubtedly the gut microbiome will be implicated in the regulation of these processes, but the detailed understanding of its role is in its infancy,

especially in relation to the cross-talk between lipids and the cells of immune system.

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Ethical conduct

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Executive summary

Influence of immune system on lipids & lipoproteins

- Adaptive immune cells and cytokines can regulate plasma lipids, presumably for energy needs, but for the most part the mechanisms are unknown.
- Regulatory T cells promote the clearance of apoB-containing lipoproteins via increasing the expression of sortilin-1 and lipid-modifying enzymes by the liver.

Lipid homeostasis in immune cells

- Lipid homeostasis in immune cells plays an important role in their expansion and function.
- For the selective expansion of the cells of both the innate and adaptive immune systems, energy provided to some extent by plasma lipids and lipoproteins and the lipid components of cell membranes are required. Lipid redistribution within membrane subdomains significantly regulates signaling within the immune cells.
- Different strategies are adopted by individual subsets of the immune cells for regulating their lipid requirements for expansion.
- Increasing cellular lipids by reducing efflux or increasing lipogenesis can promote proliferation of cells of the innate and adaptive systems as well as hematopoietic stem and multiprogenitor cells.
- Increasing the level of lipid rafts in lymphocytes alters their function, making them more responsive to activation.

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