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# Lipid metabolism in T cell signaling and function

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## Abstract

T cells orchestrate adaptive immunity against pathogens and other immune challenges, but their dysfunction can also mediate the pathogenesis of cancer and autoimmunity. Metabolic adaptation in response to immunological and microenvironmental cues contributes to T cell function and fate decision. Lipid metabolism has emerged as a key regulator of T cell responses, with selective lipid metabolites serving as metabolic rheostats to integrate environmental cues and interplay with intracellular signaling processes. Here, we discuss how extracellular, *de novo* synthesized, and membrane lipids orchestrate T cell biology. We also describe the roles of lipids as regulators of intracellular signaling at the levels of transcriptional, epigenetic, and post-translational regulation in T cells. Finally, we summarize therapeutic targeting of lipid metabolism and signaling, and conclude with a discussion of important future directions. Understanding the molecular and functional interplay between lipid metabolism and T cell biology will ultimately inform therapeutic intervention for human disease.

## Introduction

T cells are a major component of the adaptive immune system by providing defense against pathogens and tumors. Upon activation by antigens, costimulatory signals and cytokines, naïve T cells proliferate and differentiate into effector cells. Specifically, naïve $CD4^+$ T cells differentiate into conventional T helper ($T_H$) cells, including $T_H1$, $T_H2$, $T_H17$, and $T_{FH}$ cells, to mediate diverse immune functions. Naïve $CD8^+$ T cells differentiate into effector $CD8^+$ T cells to fight against infections and tumors via interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), and cytotoxic molecules. In addition, immunosuppressive $CD4^+$ regulatory T ($T_{reg}$) cells form during T cell development or are generated from naïve T cells to maintain self-tolerance, which is essential to prevent autoimmune responses but acts as a brake for tumor eradication. Therefore, there has been a great emphasis on understanding how T cell differentiation and function are programmed in different contexts, and to develop methods to harness the potent therapeutic properties of T cells.

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Author contributions

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Competing interests

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Recent evidence suggests that nutrients and metabolic programs are key regulators of T cell fate decisions[1], with lipids emerging as crucial mediators. Lipids are essential components of cellular membranes, and intracellular homeostasis of lipids is dynamically regulated by the uptake, *de novo* synthesis, and hydrolysis. Recent studies have identified the enzymatic nodes that alter lipid metabolism in T cells to promote or inhibit their functions in different disease contexts. Moreover, lipid molecules act as signaling messengers to impart their physiological and functional effects. Thus, lipid metabolism represents a key interface between physiology, chemical biology, and biochemical signaling.

In this review, we summarize how lipids contribute to T cell fate and function in different physiological and pathological settings. We first discuss the roles of extracellular lipids and intracellular lipid metabolism in orchestrating T cell fate choices in various immunological contexts and disease microenvironments. Then, we describe the functional effects of membrane lipids found in discrete subcellular compartments (e.g., plasma versus mitochondrial membrane). We also emphasize the interplay between intracellular signaling and lipid metabolism at multiple levels, including transcriptional and epigenetic regulation and post-translational modifications, in mediating T cell responses. Finally, we summarize preclinical and clinical data that support potential strategies to target lipid pathways for modulation of T cell function in disease therapy.

## Lipids shape the fate and function of T cells

It has long been appreciated that lipid-derived molecules, such as prostaglandins, play important roles in regulating T cell responses[2]. Extracellular lipids, including fatty acids (FAs) and cholesterol, are emerging as important nutrient sources for the generation of cellular energy and biomass, and as signaling mediators for innate and adaptive immune responses (Table 1). The metabolic and signaling roles of extracellular lipids in conventional T cell responses are discussed below (Figure 1). The emerging roles of lipid metabolism in γδ T cells, natural killer (NK) cells, invariant natural killer T (iNKT) cells, and B cells are described in Box 1.

### Extracellular FAs

FAs are divided into short-chain, medium-chain, long-chain and very-long-chain FAs. Short-chain FAs (SCFAs), such as propionate, acetate and butyrate, are generated by gut microbiota-derived bacterial fermentation from dietary fibers[3]. Diet high in fiber or butyrate boosts the effector function of $CD8^+$ T cells to aid in the resolution of influenza infection, which is associated with enhanced glycolytic and mitochondrial respiratory capacities[3]. Similarly, SCFAs are capable of rewiring metabolism such that activated T cells take up and oxidize more FAs, which enables their transition to memory-like $CD8^+$ T cells with long-term survival. Mechanistically, butyrate-derived acetyl-coenzyme A (acetyl-CoA) enters the tricarboxylic acid (TCA) cycle (also called Kreb's cycle) and fuels oxidative phosphorylation[4]. Thus, certain SCFAs affect both effector and memory $CD8^+$ T cell responses. In addition, CXCR6-expressing $CD8^+$ T cells from a mouse model of nonalcoholic steatohepatitis (NASH) are auto-aggressive when exposed to acetate[5]. Further, SCFAs are also important regulators of $T_{reg}$ cell differentiation and function in

the intestines[6–8], which likely contributes to intestinal tissue homeostasis. In addition, SCFAs potentiate anti-CD3-induced differentiation of $T_H1$ and $T_H17$ cells in the spleen and mesenteric lymph nodes, and IL-10-producing T cells in the intestines[9]. Thus, SCFAs play multifactorial roles in T cell responses (Figure 1a).

Most long-chain FAs (LCFAs) are obtained from dietary sources, although certain LCFAs are synthesized *de novo*. LCFA catabolism via FA oxidation (FAO) generates acetyl-CoA to fuel mitochondrial function. LCFAs such as palmitate and oleate enhance $T_H1$ and $T_H17$ cell differentiation and proliferation through the p38–MAPK pathway[10]. Accordingly, LCFAs accelerate disease progression of experimental autoimmune encephalomyelitis (EAE), an animal model of multiple sclerosis[10]. The tumor microenvironment (TME) is often high in cholesterol and FA content, which can alter the functionality of intratumoral T cells[11–13]. Uptake of lipids such as LCFAs and oxidized low density lipoprotein (LDL) by the scavenger receptor CD36 promotes the function of $T_{reg}$ cells but dampens the effector function of $CD8^+$ T cells in the TME[11–13]. Mechanistically, CD36-mediated uptake of lipids in $CD8^+$ T cells leads to increased lipid peroxidation, which promotes activation of p38–MAPK or induction of ferroptosis, both of which induce $CD8^+$ T cell dysfunction[12,13] (Figure 1a). In pancreatic ductal adenocarcinoma (PDAC), accumulation of LCFAs impairs the mitochondrial function of $CD8^+$ T cells and reduces lipid catabolism. Of note, very-long-chain acyl CoA dehydrogenase (VLCAD), the enzyme that initiates catabolism of palmitate and oleate, is downregulated in $CD8^+$ T cells from mouse models of PDAC, and overexpression of very-long-chain acyl-CoA dehydrogenase is associated with improved survival and persistence of the $CD8^+$ T cells in the TME[14]. The differential effects of LCFAs on T cell function in EAE and tumors may be related to interplay with other environment-specific signals that impart selective metabolic, functional, and cellular alterations in T cells, in line with site-specific requirements for glucose metabolism in $T_H17$ cells in the intestines and central nervous system during EAE[1,15]. Together, these studies illustrate the diverse effects of extracellular lipids on T cell biology in different contexts.

## Exogenous cholesterol and cholesterol derivatives

The levels of cholesterol and its biosynthetic intermediates profoundly alter T cell function in disease settings. For example, high abundance of plasma cholesterol disrupts T cell homeostasis, which mediates inflammation in hypercholesterolemia[16]. Moreover, cholesterol in the TME induces $CD8^+$ T cell exhaustion (a dysfunctional state defined by expression of certain coinhibitory molecules and impaired effector function) by triggering ER stress, leading to uncontrolled tumor growth[17]. Compared to IFN-$\gamma$-producing $CD8^+$ T cells, IL-9-producing $CD8^+$ T (Tc9) cells, which are potent inducers of antitumor immunity, have distinct gene profiles related to the synthesis and efflux of cholesterol, and have a lower cholesterol level. Further, cholesterol depletion enhances, and supplementation reduces, Tc9 cell generation by regulating the activity of the transcription factor liver X receptor (LXR)[18]. Similar effects are observed upon supplementation with oxysterols, which are oxidized cholesterol derivatives that can activate LXR signaling upon their intracellular accumulation[18]. Additionally, the oxysterol 7$\alpha$,25-dihydroxycholesterol also signals via EBI2 (also called GPR183) to promote localization of activated $CD4^+$ T cells to the interface between the B cell follicle and T cell zone of the spleen; this ultimately promotes $T_{FH}$

cell accumulation and induction of humoral immunity[19] (Figure 1b). Of note, LDL, which acts as a carrier for cholesterol, can be taken up by LDL receptor (LDLR). LDL depletion or LDLR deficiency impairs $CD8^+$ T cell function *in vitro* and their antitumor activity, although the antitumor effects may be partly independent of uptake for cholesterol or LDL[20]. Thus, sterols have multiple effects on T cell function that may be exploited for immunotherapies.

### Bile acids

Bile acids are cholesterol-derived metabolites that are abundant in the mammalian gut and play important roles in lipid absorption. Liver-derived bile acids are metabolically modified by intestinal microbiota to generate intestinal bile acids (especially lithocholic acid (LCA) and deoxycholic acid (DCA)). These intestinal bile acids and their derivatives serve critical functions in T cell biology. Specifically, the LCA derivative 3-oxoLCA inhibits $T_H17$ cell differentiation via binding to $T_H17$ cell-specific transcription factor ROR$\gamma$t (retinoic acid receptor-related orphan receptor $\gamma$t)[21]. In contrast, combined supplementation of LCA and its derivative 3-oxoLCA increases ROR$\gamma t^+$ peripherally derived $T_{reg}$ ($pT_{reg}$) cell accumulation via $T_{reg}$ cell-intrinsic engagement of vitamin D receptor, which limits susceptibility to intestinal inflammation and colitis[22]. The LCA derivative isoalloLCA also induces expression of the transcription factor Foxp3 and subsequent differentiation of $pT_{reg}$ cells by promoting generation of mitochondrial reactive oxygen species[21]. NR4A1, which is a nuclear hormone receptor, likely also mediates the effect of isoalloLCA on $pT_{reg}$ cells[23]. In addition, the deoxycholic acid derivative 3β-hydroxydeoxycholic acid (isoDCA) induces Foxp3 expression by inhibiting farnesoid X receptor (FXR, also called NR1H4) transcriptional activity in dendritic cells (DCs); consequently, these DCs have enhanced ability to prime $pT_{reg}$ cell differentiation from naïve $CD4^+$ T cells[24]. However, upon loss of the nuclear xenobiotic receptor CAR (encoded by *Nr1i3*), intestinal bile acids drive the proinflammatory $CD4^+$ T cell response and trigger inflammation in the lamina propria of the small intestine, owing to diminished detoxification of bile acids[25] (Figure 1c). Thus, modulation of intestinal bile acid generation or signaling may provide beneficial effects, by tuning T cells responses to improve therapy for gastrointestinal disease and possibly other inflammatory disorders.

## Intracellular reprogramming of lipid metabolism

Intracellular lipid homeostasis is balanced by lipid synthesis, catabolism and storage. Immunological signals are key regulators of lipid metabolism in T cells. T cell receptor (TCR) stimulation activates PI3K–Akt and mechanistic target of rapamycin (mTOR) signaling to induce FA and mevalonate synthesis[26,27]. Further, CD28 costimulatory signals transiently induce carnitine palmitoyltransferase-1 (CPT1a) expression before the first cell division[28]. However, CD28 costimulation upregulates TCR-dependent activation of mTORC1, an important positive regulator of effector T cell responses that promotes anabolic metabolism[29,30], suggesting temporal effects of CD28 costimulation on lipid metabolic programs (Figure 2). In this section, we discuss how intracellular lipid metabolism directs T cell differentiation and function (Table 1).

## Lipid synthesis

Activated T cells upregulate *de novo* synthesis programs that lead to the generation of FA-and mevalonate-derived lipids. FA synthesis (FAS) is orchestrated by several enzymes, including acetyl-CoA citrate lyase (ACLY), acetyl-CoA carboxylase 1 (ACC1), and fatty acid synthase (FASN) (Figure 3a). Inhibition of ACC1 reduces $T_H17$ cell differentiation[31,32] but enhances memory $CD4^+$ T cell formation[33]. ACC1 is also required for antigen-specific $CD8^+$ T cell accumulation during bacterial infection[34] and the suppressive function of $T_{reg}$ cells in the TME[35]. In addition, ACLY, which converts cytosolic citrate to acetyl-CoA, is a crucial enzyme in the regulation of FAS versus FAO. ACLY is actively degraded during the differentiation of *in vitro* Treg ($iT_{reg}$) cells, leading to a downregulation of FAS and corresponding upregulation of FAO to support $iT_{reg}$ generation[36]. Overall, these studies establish important roles for FAS in the control of T cell differentiation and function.

Ceramides are composed of sphingosine and FA, and serve as lipid messengers for intracellular signaling cascades. Ceramide synthase 6 (CerS6), which is a rate-limiting enzyme for ceramide biosynthesis (Figure 3a), facilitates expansion and function of alloantigen-specific T cells and contributes to graft-versus-host disease (GVHD) in a mouse model of allogeneic hematopoietic cell transplantation (allo-HCT) therapy. Further, CerS6-deficient T cells have impaired proliferation and IFN-γ production, which is associated with a partial reduction of GVHD but retention of graft-versus-leukemia responses in an allo-HCT model, suggesting that targeting ceramide synthesis may improve allo-HCT therapy[37]. In T cells from aged mice, ceramides accumulate in the mitochondria and promote mitophagy through inhibition of protein kinase A. Consequently, the antitumor function of aged T cells is attenuated[38]. However, treatment of liver tumor-bearing mice with nanoliposomes containing C6-ceramide results in enhanced antigen-specific $CD8^+$ T cell functionality and delayed tumor growth[39], revealing possibly T cell-extrinsic effects of exogenous ceramide at impacting antitumor function of T cells. Collectively, these studies suggest that modulation of ceramide metabolism may be useful for tuning therapies against hematological and solid tumors.

The mevalonate pathway is essential for the generation of isoprenoids, cholesterol, and cholesterol derivatives. Lipid synthesis via the mevalonate pathway requires several key enzymes, including HMG-CoA reductase (HMGCR) (Figure 3b). T cell-specific deletion of HMGCR leads to a severe reduction of peripheral T cells, while $T_{reg}$ cell-specific deletion of HMGCR is associated with the development of systemic autoimmunity[40]. HMGCR-deficient T cells have a cell-survival defect, which is rectified by the addition of mevalonate or the isoprenoid geranylgeranyl pyrophosphate (GGPP)[40,41]. Moreover, deletion of Pggt1b (enzyme for protein geranylgeranylation via GGPP) or Fntb (enzyme for protein farnesylation via farnesyl pyrophosphate or FPP) in $T_{reg}$ cells results in a profound loss of $T_{reg}$ cell-suppressive function and development of fatal autoimmunity[27], highlighting the importance of mevalonate metabolism and downstream protein prenylation (see below for more details). Similar defects in mevalonate- and GGPP-dependent $T_{reg}$ cell survival are also observed upon deletion of LKB1, a kinase that is essential to promote mevalonate biosynthesis[41] and FAO in $T_{reg}$ cells[42]. However, mTORC1 orchestrates mevalonate metabolism in $T_{reg}$ cells to establish their suppressive activity and

immunological tolerance[43], suggesting complex regulation of mevalonate metabolism in $T_{reg}$ cells that may be associated with their activation or inflammatory state. The specific deletion of HMGCR in $T_H17$ cells also protects mice from EAE[44]. Therefore, targeting of mevalonate metabolism is an attractive means to tune autoimmune and inflammatory responses mediated by $CD4^+$ T cells.

## Lipid catabolism

The induction of FAO is associated with elevated AMP-activated protein kinase (AMPK) activity (Figure 3c), which promotes the generation of central memory $CD8^+$ T cells ($T_{CM}$; a subset of memory $CD8^+$ T cells that recirculate via secondary lymphoid organs)[45,46]. Compared with effector $CD8^+$ T cells, $T_{CM}$ cells have increased FAO, which is driven by triacylglycerides that are synthesized *de novo* from glucose rather than extracellular FAs[47]. Mechanistically, intrinsic lipolysis of intracellular triacylglycerides is mediated by lysosomal acid lipase (LAL)[47] (Figure 3c). IL-15 signaling promotes upregulation of CPT1a expression to facilitate FAO[48], whereas IL-7 signaling induces glycerol uptake for triacylglyceride synthesis and FAO[49], thereby supporting memory $CD8^+$ T cell longevity (Figure 2). However, in contrast to the defective memory responses upon etomoxir treatment[45,48], genetic deletion of CPT1a in T cells does not impair memory $CD8^+$ T cell generation. Nonetheless, etomoxir treatment of CPT1a-deficient T cells reduces mitochondrial oxidative function and incorporation of extracellular palmitate into TCA cycle intermediates[50], suggesting that memory T cell generation requires mitochondrial function. Such effect may be partly mediated by short-chain or medium-chain FAs whose oxidation does not require CPT1a, glucose, or amino acids, and future studies are required to test these or additional hypotheses. In an obesity-associated breast tumor model, STAT3 activation increases FAO and impairs the effector function of $CD8^+$ T cells[51]. In contrast, although they also show $CD8^+$ T cell dysfunction, FAO-associated genes are not upregulated in $CD8^+$ T cells from an obesity-associated MC-38 tumor model[52], suggesting TME-dependent regulation of lipid metabolism in tumor-infiltrating T cells in response to obesity. Thus, FAO is associated with memory T cell generation and functionality in inflammatory contexts.

Tissue-resident memory ($T_{RM}$) cells reside in non-lymphoid tissues. Similar to the role of P2RX7 in $T_{CM}$ cells, activation of P2RX7 promotes AMPK signaling, mitochondrial function and accumulation of $T_{RM}$ cells[46]. Moreover, extracellular lipid uptake by $T_{RM}$ cells is increased compared with other memory T cell populations *in vitro*, and inhibition of CPT1a or FAO reduces the accumulation of skin $T_{RM}$ cells *in vivo*[53]. Also, deficiency in FA-binding proteins (FABPs) 4 and 5, which act as complex regulators of lipid transport and trafficking in cells, impairs mitochondrial oxygen consumption and virus-specific $T_{RM}$ cell accumulation in the skin[53], whereas FABP1 is important for $T_{RM}$ accumulation in the liver[54]. Thus, FABPs orchestrate extracellular FA uptake to promote FAO for $T_{RM}$ generation or survival. Metabolic reprogramming toward FAO also prolongs $T_{RM}$ cell longevity, which is associated with enhanced antitumor immunity in gastric adenocarcinoma[55]. Finally, $T_{reg}$ cells express FABP5, which is important to restrain mitochondrial DNA-induced type I IFN signaling and downstream IL-10 production in $T_{reg}$ cells[56]. Collectively, FAO and FABPs tune T cell responses in tissue microenvironments, including tumors.

### Lipid storage

Lipid droplets are an intracellular lipid storage depot, which are utilized by effector memory $CD4^+$ T cells in nutrient-depleted environments[57] such as the TME. Lipid droplets are also dynamically regulated in certain T cell subsets in nutrient-replete environments. The effector memory population of $CD4^+$ T cells contain fewer lipid droplets than other $CD4^+$ memory T cell subsets[57]. Also, $T_{reg}$ cells have enhanced lipid droplet content compared to conventional T cells[58]. Lipid droplet formation is mediated by diacylglycerol acyl transferase 1 (DGAT1) (Figure 3d), and DGAT1 inhibition impairs Foxp3 induction, suggesting a role for lipid droplets in $T_{reg}$ cell formation or maintenance[58]. Moreover, senescent T cells, which are in a dysfunctional state, in the TME display alterations in the composition of lipid species and droplet accumulation that is related to elevated group IVA phospholipase $A_2$ activity. Inhibition of such activity reverses T cell senescence, thereby reducing tumor size and extending the survival of tumor-bearing mice[59]. Therefore, understanding the role of lipid droplets in T cell subsets and how to modulate lipid droplet-related metabolism may give rise to effective therapies for cancer and other diseases.

## Regulation of T cell function by membrane lipids

The activation of T cells is associated with profound changes in the composition, distribution, and dynamics of membrane lipids. These processes affect T cell differentiation and function in different physiological contexts as discussed below (Figure 4 and Table 1).

### Membrane lipids transmit intracellular signaling

The plasma membrane is composed of various lipid molecules, which form heterogenous domains that act as signaling platforms. For example, specific lipids recruit signaling proteins that contain lipid-binding domains to the plasma membrane, such as the pleckstrin homology domain of Akt that binds to phosphatidylinositol 3,4,5-triphosphate (PIP3) to induce downstream signaling. Notably, TCR signaling, in combination with costimulation and IL-2 signaling, activate phosphatidylinositol-3-kinase (PI3K) to increase PIP3 generation from phosphatidylinositol 4,5-bisphosphate (PIP2), and this reaction is opposed by the lipid phosphatase and tumor suppressor PTEN[29].

Lipids also function as second messengers with important immune-regulatory functions. Following TCR engagement, phospholipase C (PLC) hydrolyzes PIP2 to generate inositol trisphosphate (IP3) and diacylglycerol (DAG). IP3 and DAG act as signaling mediators to promote calcium release from intracellular stores and drive protein kinase C (PKC) activation, respectively. These events lead to activation of the transcription factors NFAT and NF-κB that are important for T cell functionality. The DAG-dependent signaling pathway is terminated by diacylglycerol kinase (DGK), which converts DAG to phosphatidic acid (PA). DGK-deficient antigen-specific $CD8^+$ T cells show enhanced expansion and increased cytokine production, which enhances viral clearance. However, DGK-deficient memory $CD8^+$ T cells have impaired expansion after viral re-challenge, suggesting opposing roles for DGK in effector and memory $CD8^+$ T cells[60] (Figure 4a).

### Lipids spatially coordinate immune receptor signaling

The immunological synapse is a specialized structure that forms in the plasma membrane when TCRs and costimulatory molecules expressed on T cells bind their ligands on antigen-presenting cells. The immunological synapse serves important spatiotemporal roles in signal integration to tune T cell activation and function. Increasing the level of cholesterol in the plasma membrane through inhibition of ACAT1, a cholesterol esterification enzyme, enhances TCR clustering, maturation of the immunological synapse, and promotes cytolytic granule secretion in $CD8^+$ T cells[61]. These alterations cause ACAT1-deficient $CD8^+$ T cells to exhibit better antitumor effect. Moreover, cholesterol sulfate, which is a natural analog of cholesterol, impinges upon TCR signaling and triggers apoptosis in double-positive thymocytes undergoing positive selection[62]. Together, these results show that lipids are important mediators of activation-associated signaling events in T cells.

### Context-specific regulation of membrane lipids

Recent studies have uncovered context-dependent roles for membrane lipid species in the regulation of T cell responses. Phosphatidylethanolamine (PE) is an essential phospholipid in the plasma membrane that is *de novo* synthesized via the CDP–ethanolamine pathway. CDP–ethanolamine pathway-dependent PE synthesis selectively promotes $T_{FH}$ cell generation to drive humoral immunity, with such regulation associated with PE distribution to the outer layer of $T_{FH}$ cell membrane and stabilization of surface CXCR5 expression[63] (Figure 4b). Another phospholipid, cardiolipin, is synthesized and localized in inner mitochondrial membrane, and its *de novo* synthesis maintains $CD8^+$ T cell function. Accordingly, T cells lacking PTPMT1 (protein tyrosine phosphatase mitochondrial 1), an enzyme essential for cardiolipin synthesis, respond poorly to antigenic stimulation and have impaired mitochondrial fitness that limits memory T cell differentiation[64] (Figure 4c). Therefore, lipid synthetic pathways regulate context-dependent T cell responses, suggesting that membrane lipids may serve as actionable targets to tune T cell functionality in different diseases.

## Lipids are metabolic rheostats of intracellular signaling

Lipids serve as central regulators of intracellular signaling processes at the transcriptional, epigenetic and post-translational levels. We summarize below recent advances of understanding the roles of lipids as signaling molecules, with a particular emphasis on lipid-dependent post-translational modifications (Figure 5 and Table 1).

### Lipids as metabolic modulators of gene transcription

Lipids bind to and influence the activation of transcription factors that affect T cell responses, including nuclear receptors peroxisome proliferation-activated receptors (PPARs) and LXRs. Specifically, FAs activate PPARs, and cholesterol and other sterols activate LXRs. Gain- and loss-of-function studies suggests that PPARs play complex roles in conventional T cell differentiation[65]. Also, deficiency of PPARγ impairs the accumulation and function of $T_{reg}$ cells in visceral adipose tissue (VAT)[66], and as such contributes to systemic metabolic homeostasis. LXR signaling impairs T cell activation by inhibiting lipid and cholesterol synthesis via antagonism of the sterol regulatory binding proteins

(SREBPs)[67], which are discussed more below. However, LXRs can play both pro- and anti-inflammatory roles in T cell-driven disease severity. For instance, treatment with pharmacological agonists of LXRs dampens MOG-induced pathogenic $T_H17$ cell differentiation *in vitro* and alleviates disease severity of EAE[68] associated with reduced $T_H17$ cell effector cytokines *in vivo*, while oxysterols, which are natural ligands that activate LXRs, inhibit IL-10 production by anti-inflammatory type 1 regulatory cells[69]. Overall, these complex roles of PPARs and LXRs appear to be dependent on the disease or tissue context and the subset of T cells analyzed.

SREBPs promote lipid synthesis and require SREBP cleavage-activating protein (SCAP) for activation. SCAP–SREBP signaling drives reprogramming of lipid metabolism toward synthesis and uptake, which causes T cells to exit from their quiescent state and undergo cellular proliferation[26]. Further, the SCAP–SREBP axis coordinates FA and mevalonate metabolism to promote the functional maturation and immunosuppressive function of $T_{reg}$ cells in the TME. Loss of SCAP or FASN in $T_{reg}$ cells results in the loss of suppressive function selectively in the TME, leading to enhanced tumor clearance[35]. Understanding the relationship between lipids and transcriptional programming in different contexts may provide insight for therapeutic targeting of T cells in diverse diseases.

FAO-derived acetyl-CoA can also be used as a substrate for histone acetyltransferases to promote histone acetylation. Indeed, acetate induces histone acetylation to promote IFN-γ production from $CD8^+$ T cells in glucose-limiting conditions[70] and promotes GAPDH acetylation and activation to augment glycolysis and recall responses of memory $CD8^+$ T cells during acute viral infection[71]. Further, butyrate suppresses the activity of histone deacetylases, thereby boosting the effector function of $CD8^+$ T cells[72]. Butyrate also enhances histone acetylation of Foxp3 and differentiation of $T_{reg}$ cells[6,7]. Consistent with the importance of acetyl-CoA in T cell responses, ACLY, which catalyzes synthesis of acetyl-CoA, is a positive regulator of histone acetylation and T cell immunity. Inhibition of ACLY impairs the function and proliferation of $T_H1$ cells associated with reduced histone H3K9 acetylation[73]. Thus, acetyl-CoA serves context-dependent roles in epigenetic regulation. Future work is required to ascertain the signals that contribute to ACLY-dependent lipid synthesis versus histone acetylation, as well as the roles of these ACLY-dependent processes in fate decisions.

## Post-translational modifications for modulation of intracellular signaling

Bidirectional metabolic signaling, which is the two-way communication between intracellular signaling networks and cell metabolic programs, is emerging as a crucial regulator of T cell responses[29], with lipid modifications serving a key node underlying these processes. Certain lipid metabolites are post-translationally attached to proteins at specific amino acid residues to alter protein stability or membrane localization for modulation of T cell function (Figure 5a). For example, mevalonate pathway-derived isoprenoids farnesyl pyrophosphate (FPP) and GGPP are important for protein prenylation linked to specific cysteine residues of certain small G proteins such as the RAC family[74]. Inhibition of the mevalonate pathway or protein prenylation limits the activation, proliferation, survival and effector function of T cells[74]. Protein prenylation also controls the accumulation of

activated $T_{reg}$ cells (also called effector $T_{reg}$ cells) by interplaying with immune receptor signaling that promotes the differentiation, proliferation and survival of $T_{reg}$ cells to prevent autoimmune reactions[27]. Further, downstream of SCAP–SREBP signaling, GGPP-mediated protein geranylgeranylation drives expression of the immune checkpoint molecule PD-1 to support the suppressive function of intratumoral $T_{reg}$ cells[35] (Figure 5b). Therefore, post-translational modifications represent a regulatory axis that links lipid metabolism to intracellular signaling, which may be used as therapeutic targets for T cell-mediated diseases.

Additional lipid post-translational modifications, including palmitoylation and myristoylation, are implicated in T cell immunity. Palmitoylation is the process by which palmitate is conjugated to cysteine on a thioester linkage. Recent studies show that the palmitoyl acyltransferase DHHC18 promotes the palmitoylation of VAMP7 (a protein that is essential for intracellular vesicle fusion), thereby facilitating VAMP7 recruitment to the immunological synapse upon TCR activation to propagate TCR signaling[75]. Moreover, myristoylation occurs when the FA myristate is attached to glycine residues in proteins. One of the myristoylation targets is AMPK[76] (Figure 5a), which has roles in memory T cell formation as discussed above[45,46]. Functional defect in N-myristoyltransferase, which mediates myristoylation, in T cells from rheumatoid arthritis impedes AMPK activity and instead, drives hyperactive mTOR and uncontrolled differentiation of $T_H1$ and $T_H17$ cells[76] (Figure 5b). Thus, lipids are crucial modulators of intracellular signaling and play diverse roles in distinct T cell subsets (summarized in Table 1).

## Targeting lipid metabolism in T cells for disease therapy

Given the important roles of T cells in human disease, there is growing interest in targeting T cells for disease therapy. Here, we highlight approaches to target lipid metabolism or signaling, and also summarize these studies in Table 2.

### Chemicals targeting of lipid metabolism or signaling alter T cell biology

Several inhibitors that target enzymes in lipid-related metabolic pathways have been developed (Table 2 and Figure 5a), with complementary genetic and chemical targeting approaches demonstrating their specificity and applicability to modulate T cell function. As noted above, etomoxir irreversibly inhibits CPT1a to suppress FAO, with etomoxir treatment inhibiting the survival or differentiation of $T_{reg}$ and memory T cells[45,50]. However, genetic deletion of CPT1a does not alter the homeostasis of $T_{reg}$ or memory T cells *in vivo*[50,77]. Instead, etomoxir treatment *in vivo* reduces mitochondrial respiration independent of CPT1a-mediated FAO[50]. Whether these effects are attributed to inhibition of CPT1a-independent oxidation of SCFAs or MCFAs, or other CPT isoforms that may promote FAO, remains uncertain. Similar to genetic deletion, pharmacological inhibition of HMGCR using statins impairs conventional T cell and $T_{reg}$ expansion and function[27,40,41]. Moreover, inhibition of protein farnesylation with a farnesyltransferase inhibitor (FTI) partially phenocopies the cellular features of statin-treated $T_{reg}$ cells, while suppression of protein geranylgeranylation using a geranylgeranyltransferase inhibitor (GGTI) fully recapitulates the statin-induced effects[27]. Additionally, both statin and GGTI treatments

increase KLF2 expression that modulates inflammatory and pathogenic $CD8^+$ T cells[78]. It would be insightful to examine the relative effects of inhibitors targeting the mevalonate pathways in individual cell types, given the central importance of this pathway in cellular physiology.

Studies have also begun to explore the effects of FAS-related inhibitors on T cell function. Inhibition of ACC1 by TOFA during early T cell priming enhances the pool of memory T cells in chronic parasitic infection[79], which is consistent with genetic evidence in ACC1-deficient T cells in some systems[33], with the caveat that ACC1 may be important for survival that maintains memory T cells over time[34]. Also, TOFA treatment limits $T_H17$ and increases $T_{reg}$ cell generation[31], with ACC1 deletion also reducing $T_H17$ cell differentiation, especially in an obese environment, with no notable effects on $T_{reg}$ cell differentiation[32]. Treatment of human $CD4^+$ T cells with the FASN inhibitor C75 prevents activation-induced cell death of effector cells[80]. However, aside from a role in intratumoral $T_{reg}$ cells[35], genetic deletion of FASN in conventional T cells has not been explored. Comparative analyses of the effects of pharmacological and genetic perturbations of FASN will be insightful for identifying possible off-target or toxic effects of FASN inhibitors in T cells, and for potential clinical applications to modulate T cell responses in disease.

Lipid agonists that promote PPARs also modulate T cell fate. For instance, the PPARγ ligand ciglitazone enhances the conversion of naïve $CD4^+$ T cells into $T_{reg}$ cells[81]. Further, pioglitazone, another PPARγ ligand, enhances $T_{reg}$ cell accumulation in the VAT[66], while the PPARα agonist gemfibrozil skews naïve $CD4^+$ T cell differentiation in favor of $T_H2$ cells[82]. Collectively, lipid agonists may be instrumental for altering T cell subset differentiation.

## Targeting lipid metabolism or signaling for disease therapeutics

Targeting lipid pathways or molecules in T cells holds enormous therapeutic potential (Table 2). In particular, modulation of lipid uptake or metabolism alters the antitumor function of T cells in mouse models of cancer[11–14,17,35,59]. In addition, treatment with GW0742, an agonist of PPARβ/δ, mitigates EAE[83]. The generation of specific lipids or induction of lipid metabolic pathways promote $T_{reg}$ cell generation and function, which may also be applied to the treatment of autoimmune diseases, including multiple sclerosis and type 1 diabetes[84,85]. Moreover, microbiota-derived lipids mitigate disease in a murine model of GVHD by modulating T cell responses[86]. Similarly, an interplay between the microbiome, dietary fiber, and SCFAs influences the response to cancer immunotherapies. Enhanced anti-PD-1 therapeutic responses are observed in melanoma patients with high microbiome diversity and an abundance of certain microbiota species, including *Ruminococcaceae, Faecalibacterium, Bifidobacterium longum*, *Collinsella aerofaciens*, and *Enterococcus faecium*[87,88]. In addition, reconstitution of germ-free mice with fecal material from anti-PD-1 responding patients improves tumor control and anti-PD-L1 therapy that is associated with enhanced T cell responses[88]. Moreover, higher intake of dietary fiber is correlated with improved responsiveness to immune checkpoint blockade treatment in melanoma patients[89]. The precise role of microbiota-derived SCFAs in reprogramming T cell metabolism and the effects on the antitumor response warrant further investigation.

Several lipid metabolism-related drugs are also being explored for clinical use (Table 2). Treatment with statins impedes the growth and survival of certain tumors. Moreover, statins are being explored for use in combination therapies for anticancer treatments, as reviewed elsewhere[90]. The ACC1 inhibitor PF-05221304 is being explored as a treatment for NASH and nonalcoholic fatty liver disease[91]. Due to certain adverse effects associated with statin treatment, novel drugs to decrease lipid content in patients with dyslipidemia or hypercholesterolemia have been developed, including inclisiran, bempedoic acid and icosapent ethyl[92]. These drugs inhibit PCSK9, whose expression in tumor cells hinders LDLR surface level and TCR signaling in intratumoral T cells[20], further highlighting the clinical potential to target lipid metabolism.

## Conclusions and future outlook

As summarized in this review, lipids are remarkably diverse and have crucial roles in the regulation of energy or biomass production, membrane structure, and signal transduction in T cells. By integrating immunological and environmental cues, T cells undergo rewiring of metabolic programs including intracellular lipid synthesis and extracellular lipid uptake and utilization, which contribute to their functional specialization and adaption by modulating metabolic and signaling events. Consequently, perturbation of lipid metabolism alters T cell responses in different physiological states and diseases. Therefore, lipid metabolism-based therapy offers an attractive means to modulate T cell function for the treatment of human disease.

Several key questions and directions remain to be explored regarding the roles of lipid metabolism and signaling in T cells. First, how do immune receptor-mediated processes orchestrate uptake, anabolism, catabolism and storage of lipids in discrete T cell subsets? Second, does nutrient competition or coordination between cell types in a microenvironment influence the acquisition of extracellular lipids by T cells in different contexts? Third, what role do environmental cues, including macronutrients (e.g. glucose or amino acids), cytokines, growth factors, and oxygen levels, play in modulating lipid metabolism to instruct T cell fate decisions? Finally, it will be essential to reconstruct T cell-specific lipid signaling networks, including signals that shape lipid metabolic rewiring and the downstream programs tuned by lipids at the transcriptional, epigenetic, and post-translational levels. These investigations will allow for the development of lipid-based therapies to target specific subsets of T cells in discrete settings and contexts.

Although context-dependent regulation of lipid metabolism is emerging for T cell responses[63,64], lipid metabolism is a central biological process wherein conventional targeting methods, such as small molecule inhibitors, may lead to non-specific or adverse effects. Therefore, strategies to target lipid metabolic processes selectively in T cells will be of critical importance to exploit. Antibodies have high specificity and affinity for their ligands, and these can be conjugated to small molecules or nanoparticles to achieve site- or cell type-specific targeting of T cell subsets. Also, technologies that predict the molecular targets of lipid signaling, including the integration of advanced computational tools, machine learning, and robotic-aided high-throughput screening[93], will likely rapidly advance drug development to target lipid metabolism. The combined use of innovative technologies and

targeting strategies to modulate lipid metabolism or signaling is anticipated to advance next-generation therapies.

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**Box 1.**

### Lipid metabolism of additional lymphocytes in disease contexts

Lipid metabolism orchestrates the function of multiple lymphocyte populations to modulate immune responses. γδ T cells and NK cells have crucial roles in protective immunity against tumors and viral infections. IL-17$^{+}$ γδ T cells are expanded in obesity and display high capacity for lipid uptake and storage, associated with enhanced tumor growth[94]. Conversely, NK cell functions are impaired in fatty-acid-rich environments, such as obesity and certain TMEs, which occurs due to activation of PPARs[95,96]. iNKT cells are CD1d-restricted T cells that share features of both innate and adaptive immune cells. iNKT cells express PPAR-γ, which induces lipid metabolism and especially cholesterol synthesis to promote the activation, proliferation and antitumor function of iNKT cells[97]. In contrast, high levels of extracellular lipids suppress inflammatory cytokine production by iNKT cells in a murine model of rheumatoid arthritis[98]. B cells are adaptive immune cells specialized in antibody production. Glutathione peroxidase-4 is required for the maintenance of antibody responses by preventing lipid peroxidation and ferroptosis in B cells, which is associated with increased lipid metabolism[99]. IL-10-producing regulatory B cells restrict immune and inflammatory responses, and such regulatory function is dependent upon mevalonate metabolism. B cells from patients with mevalonate kinase deficiency, an inherited autoimmune disorder, have poor IL-10 induction, which is restored by exogenous GGPP treatment[100]. Thus, lipid metabolism regulates multiple facets of adaptive immune responses that may be targetable for disease treatment.

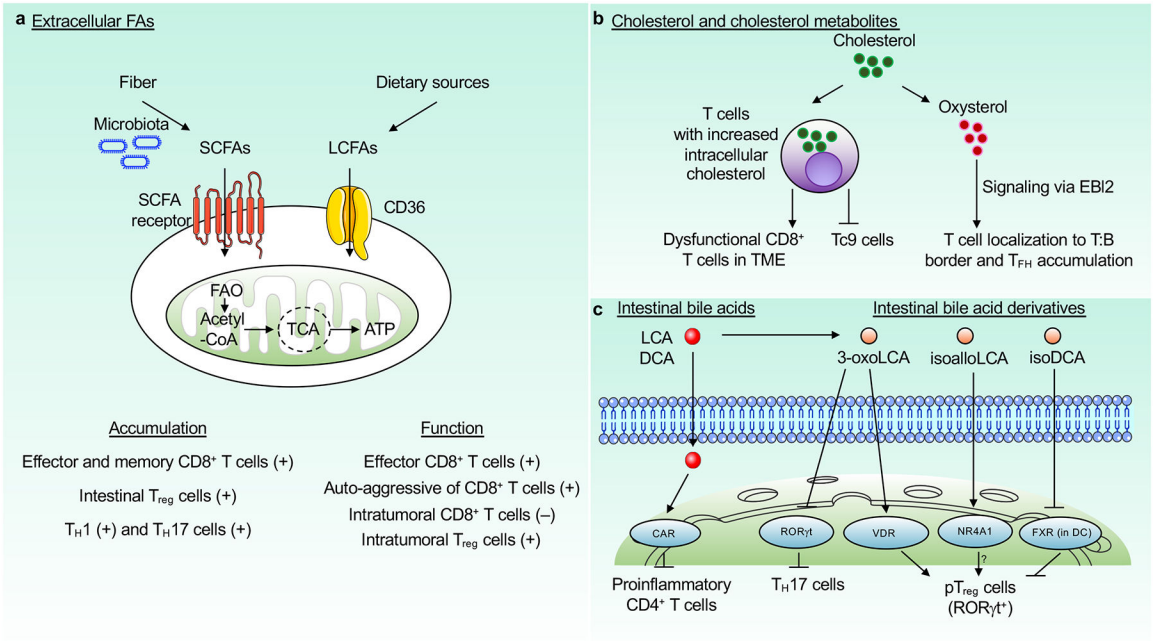


**Figure 1. Extracellular lipids in T cell differentiation and functional adaptation.**

Extracellular lipids, such as FAs, cholesterol or cholesterol-derived metabolites, and bile acids regulate multiple aspects of T cell biology. **a,** SCFAs, which are derived from dietary fiber via microbiota-dependent fermentation, regulate T cell accumulation and function. Exogenous LCFAs such as oleic acid are taken up via CD36 from the TME and impair the function of $CD8^+$ T cells but enhance the function of $T_{reg}$ cells. **b,** T cells take up cholesterol from the TME, which inhibits the function of $CD8^+$ T cells. Cholesterol accumulation also impedes Tc9 cell generation. Oxysterols signal via EBI2 to promote migration of T cells to the T cell–B cell border and contribute to $T_{FH}$ cell generation. **c,** Intestinal bile acids (lithocholic acid (LCA) and deoxycholic acid (DCA)) and their derivatives (3-oxoLCA, isoalloLCA, and isoDCA) modulate T cell differentiation and maintenance. 3-oxoLCA inhibits $T_H17$ and promotes $pT_{reg}$ (marked by RORγt expression) cell differentiation, by binding to RORγt and vitamin D receptor (VDR), respectively. IsoalloLCA promotes $pT_{reg}$ cell differentiation, likely in an NR4A1-dependent manner. IsoDCA promotes $pT_{reg}$ cell differentiation by suppressing FXR activity in dendritic cells (DCs). Intestinal bile acids are detoxified by constitutive androstane receptor (CAR) to prevent activation of proinflammatory $CD4^+$ T cell response. FAs, fatty acids; SCFAs, short-chain FAs; LCFAs, long-chain FAs; TME, tumor microenvironment. Receptors, mitochondrial, and nuclear structures used in this and other figures were obtained from Servier Medical Art website (http://smart.servier.com).

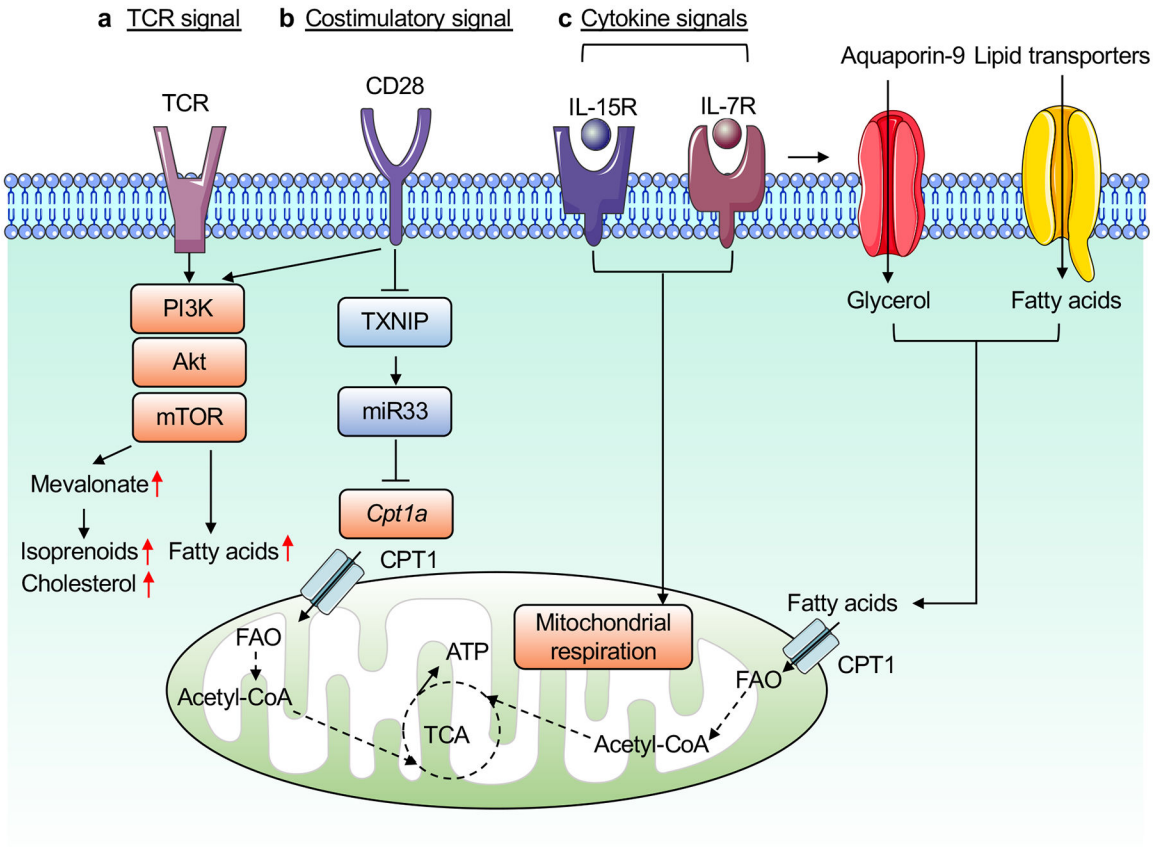


**Figure 2. Regulation of lipid metabolism by immunological signals.**

A summary of immunological signals for the regulation of lipid metabolism in T cells. **a**, Upon TCR engagement, T cells activates PI3K–Akt and mTOR signaling to induce FA synthesis and mevalonate metabolism. **b**, CD28 costimulation induces transient expression of CPT1a through thioredoxin-interacting protein (TXNIP) and miR33 (before first cell division), and may enhance mevalonate and lipid synthesis by boosting TCR-dependent mTORC1 activation. **c**, The cytokines IL-15 and IL-7 induce FAO, in part by enhancing expression of CPT1a and mediating glycerol uptake via aquaporin-9, respectively, to maintain mitochondrial respiration.

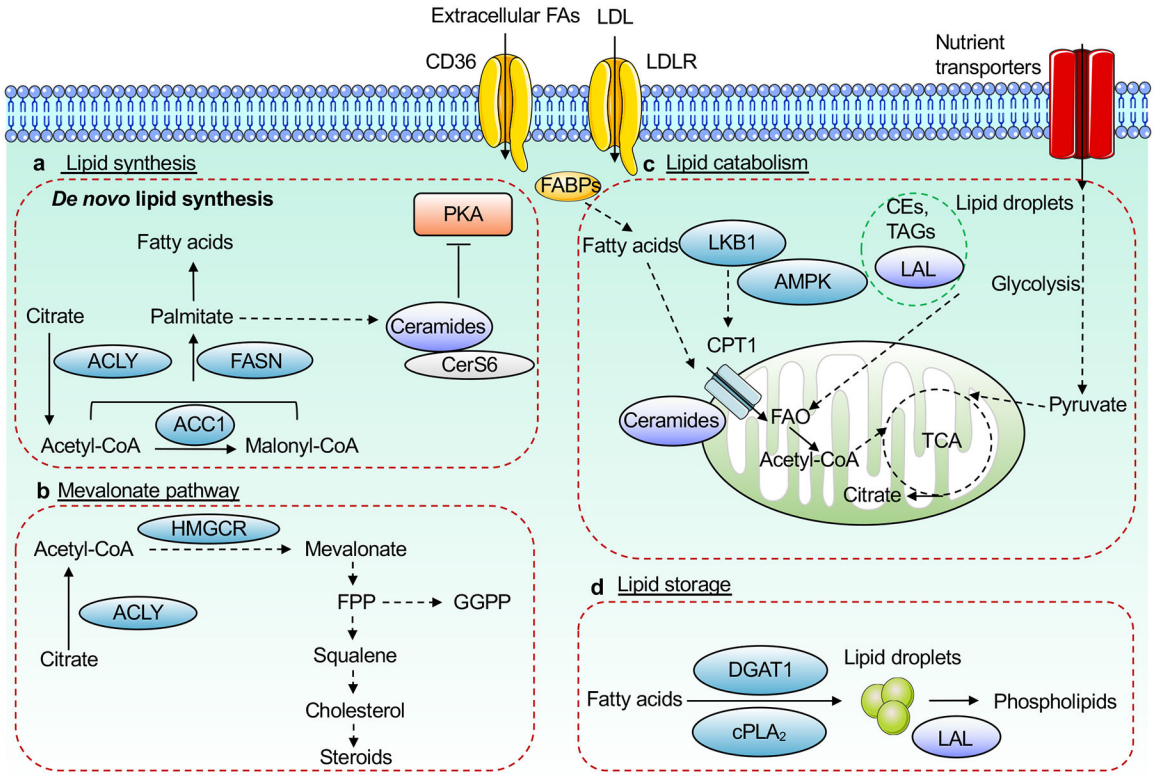


**Figure 3. Intracellular lipid metabolism in T cells.**

Intracellular lipid homeostasis is regulated by *de novo* lipid synthesis via the fatty acid (FA) and mevalonate pathways, catabolism, storage, and uptake (via specific transporters such as CD36 and LDLR). **a**, **b**, For *de novo* synthesis to occur, nutrients are catabolized into acetyl-CoA, which is used for synthesis of various FAs (via the enzymatic actions of ACLY, ACC1 and FASN, among others), ceramide (via CerS6), which suppresses PKA signaling (**a**), or mevalonate and downstream metabolites such as cholesterol and isoprenoids (via the mevalonate pathway including the rate-limiting enzyme HMGCR) (**b**). **c**, Lipid catabolism is initiated by FAO in the mitochondria, which is used to generate energy in certain T cell subsets. FAO can be mediated by exogenous lipids, whose intracellular levels are regulated by surface transporters (such as CD36 and LDLR) or intracellular FABPs, or lipid droplet-derived TAGs, which is mediated by LAL-dependent lipolysis. **d**, Lipid droplets form via $cPLA_2$ or DGAT1-dependent mechanisms to store excess levels of triacylglycerides (TAGs) and cholesterol esters (CEs). TAGs and CEs stored in these lipid droplets undergo hydrolysis via LAL to generate phospholipids. CerS6, ceramide synthase 6; ACC1, acetyl-CoA carboxylase 1; FASN, FA synthase; PKA, protein kinase A; FABPs, FA binding proteins; LAL, lysosomal acid lipase; FAO, FA oxidation; HMGCR, HMG-CoA reductase; DGAT1, diacylglycerol acyltransferase 1; $cPLA_2$, group IVA phospholipase $A_2$.

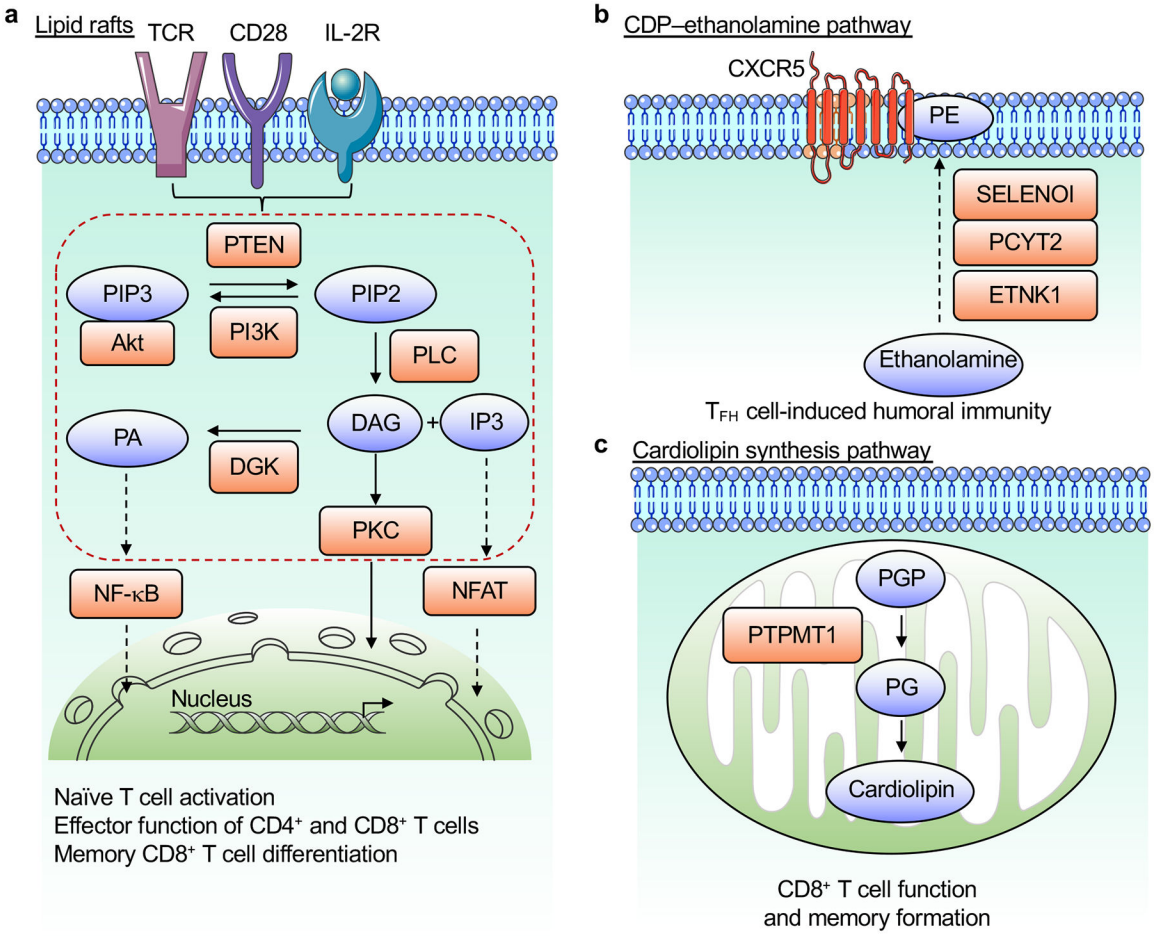


**Figure 4. Membrane lipids coordinate signaling in T cells.**

**a,** Antigens, costimulatory signals and IL-2 stimulation induce PI3K activation that generates PIP3 from PIP2, which is opposed by PTEN. Immunological signals induce PLC activation to produce DAG and IP3 from PIP2. These lipid molecules activate several signaling cascades, including those downstream of PKC, to promote activation of NFAT and NF-κB in the nucleus. DGK opposes DAG-dependent signaling by converting DAG to PA. These lipid-coordinated signaling events play multiple roles in T cell biology. **b,** *De novo* PE synthesis via the CDP–ethanolamine pathway, mediated by the enzymes ETNK1, PCYT2, and SELENOI, selectively regulates PE localization to the outer layer of the $T_{FH}$ cell membrane and promotes humoral immunity. **c,** *De novo* cardiolipin synthesis in the mitochondria, which depends upon PTPMT1, promotes the function and memory differentiation of $CD8^+$ T cells. DAG, diacylglycerol; IP3, inositol trisphosphate; DGK, diacylglycerol kinase; PA, phosphatidic acid; PIP2, phospholipid phosphatidylinositol 4,5-bisphosphate; PIP3, phosphatidylinositol 3,4,5-triphosphate; PKC, protein kinase C; PLC, phospholipase C; PE, phosphatidylethanolamine; PGP, phosphatidylglycerophosphate; PG, phosphatidylglycerol; PTPMT1, protein tyrosine phosphatase mitochondrial 1.

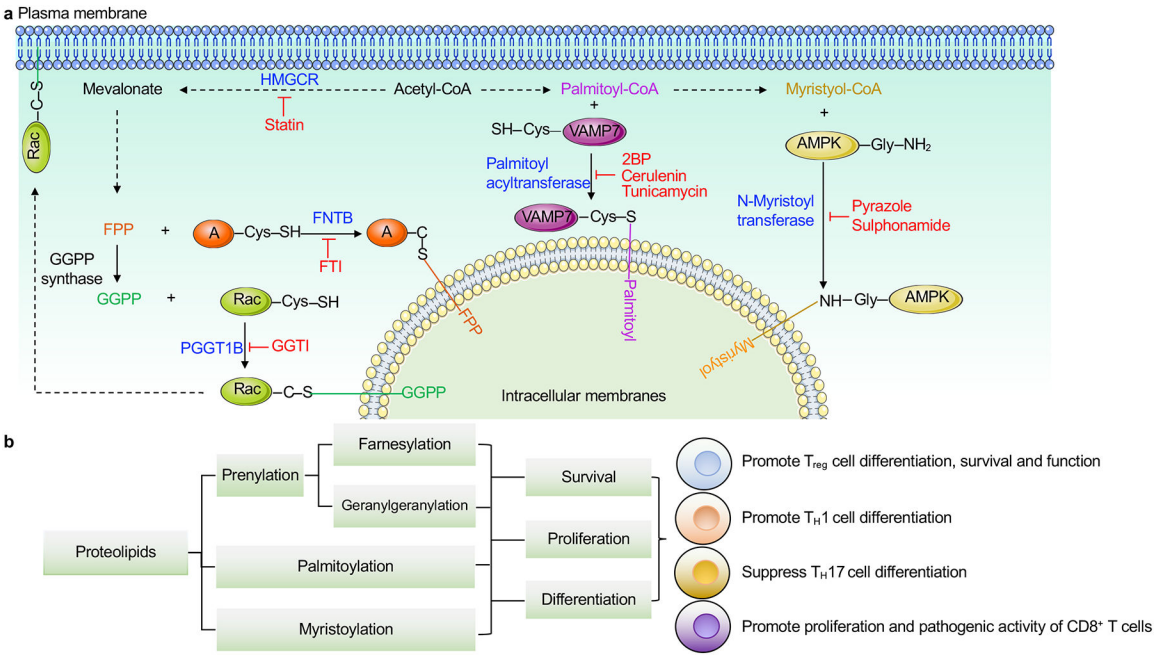


**Figure 5. Lipid-dependent post-translational modifications orchestrate T cell responses.**

**a,** A summary of lipid-dependent post-translational modifications in T cells. Acetyl-CoA is used for synthesis of either mevalonate or FAs. Mevalonate-derived farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP) are covalently linked to specific cysteine residues in small G proteins, such as via Fntb-dependent protein farnesylation that attaches FPP to target proteins (denotated as A in the figure), and Pggt1b-dependent protein geranylgeranylation that conjugates GGPP to Rac. FA-derived palmitoyl-CoA and myristoyl-CoA are conjugated to glycine resides of certain proteins important for T cell biology. For example, palmitoyl acyltransferase DHHC18 promotes protein palmitoylation of VAMP7, while N-myristoyltransferase NMT leads to protein myristoylation of AMPK. These modifications serve important roles in establishing the localization of target proteins for the propagation of intracellular signaling. Inhibitors for the different lipid transferases are shown in red. **b,** Lipid-mediated post-translational modifications play critical roles in the survival, proliferation and differentiation of T cell subsets, including $T_{reg}$, $T_H1$, $T_H17$, memory and effector T cells, as summarized in more detail in the figure. AMPK; AMP-activated protein kinase, GGTI; geranylgeranyl transferase type-1 inhibitor, FTI; farnesyltransferase inhibitor, HMGCR; HMG-CoA reductase, 2BP; 2-brompalmitate.

**Table 1.**

Overview of lipid metabolism in T cell subsets

| Lipid source or function | Lipids | Cell type | Ref. |
|---|---|---|---|
| Lipids in microenvironment | SCFAs | Effector, memory-like, or CXCR6$^+$ CD8$^+$ T cell (+), $T_{reg}$ (+), $T_H1$ (+), $T_H17$ (+) | 3–9 |
| | LCFAs | $T_H1$ (+), $T_H17$ (+), $T_{reg}$ (+), and intratumoral CD8$^+$ T cell (−) | 10–14 |
| | Cholesterol | Exhausted CD8$^+$ T cell (+) and Tc9 (−) | 17,18 |
| | Oxysterols | $T_{FH}$ (+) | 19 |
| | Bile acids | $T_H17$ (−), $T_{reg}$ (+), $pT_{reg}$ (+), and proinflammatory CD4$^+$ T cell (+) | 21–25 |
| Intracellular programs | *De novo* lipid synthesis | $T_H17$ (+), memory CD4$^+$ T cell (−), antigen-specific CD8$^+$ T cell (+), $T_{reg}$ (+), and $iT_{reg}$ (−) | 31–36 |
| | Ceramide | Antigen-specific CD8$^+$ T cell (+) | 39 |
| | Mevalonate pathway | Conventional T cell (+), $T_{reg}$ (+), and $T_H17$ (+) | 40–44 |
| | Mitochondrial fitness (lipid catabolism?) | $T_{CM}$ (+) and $T_{RM}$ (+) | 45–49 |
| | FABPs | $T_{RM}$ (+) and $T_{reg}$ (−) | 53–56 |
| | Lipid droplets | $T_{reg}$ (+), CD4$^+$ T cell (−), and CD8$^+$ T cell (−) | 58,59 |
| Membrane lipids | Phosphatidic acid | Antigen-specific CD8$^+$ T cell (−) and memory CD8$^+$ T cell (+) | 60 |
| | Phosphatidylethanolamine | $T_{FH}$ (+) | 63 |
| | Cardiolipin | CD8$^+$ T cell (+) | 64 |
| Signaling | PPARs and LXRs | VAT $T_{reg}$ (+) and $T_H17$ (−) | 66,68 |
| | SREBPs | CD8$^+$ T cell (+) and intratumoral $T_{reg}$ (+) | 26,35 |
| | FAO-derived acetyl-CoA | Effector or memory CD8$^+$ T cell (+), $T_{reg}$ (+), and $T_H1$ (+) | 70–73 |
| | FPP and GGPP | $eT_{reg}$ (+) | 27 |
| | N-myristoyltransferase | Proinflammatory $T_H1$ (−) and $T_H17$ (−) | 76 |

Positive (+) or inhibitory (–) role in differentiation, persistence, or function of the indicated T cell subset (see main text for more details). CerS6, ceramide synthase 6; $eT_{reg}$, effector $T_{reg}$; FABPs, fatty acid binding proteins; FPP, farnesyl pyrophosphate; GGPP, geranylgeranyl pyrophosphate; $iT_{reg}$, *in vitro*-derived $T_{reg}$; LCFAs, long-chain fatty acids; LXRs, liver X receptors; PPARs, peroxisome proliferation activating receptors, SCFAs, short-chain fatty acids; SREBPs, sterol regulatory binding proteins; VAT, visceral adipose tissue.

**Table 2.**

Targeting lipid metabolism in T cells for the treatment of diseases.

| Inhibitor or small molecule | Lipid category | Target | Function of target | T cells affected | Disease context | Ref. |
|---|---|---|---|---|---|---|
| Preclinical models | | | | | | |
| Etomoxir | Catabolism | CPT1a | FAO | $iT_{reg}$ and memory T cells | EAE | 50 |
| TOFA | Anabolism | ACC1 | Synthesis of FAs | Memory T cells | Chronic infection | 79 |
| C75 | Anabolism | FASN | Synthesis of FAs | Effector T cells | N/A | 80 |
| Statin | Anabolism | HMGCR | Synthesis of mevalonate | $T_{reg}$ and $CD8^+$ T cells | EAE | 27,78 |
| FTI | Post-translational modification | Fntb | Protein farnesylation | $T_{reg}$ cells | N/A | 27 |
| GGTI | Post-translational modification | Pggt1b | Protein geranylgeranylation | $T_{reg}$ and $CD8^+$ T cells | Autoimmune colitis | 27,78 |
| Ciglitazone | Agonist | PPARγ | Transcription factor | $iT_{reg}$ cells | N/A | 81 |
| Pioglitazone | Agonist | PPARγ | Transcription factor | VAT $T_{reg}$ cells | High fat diet-fed obese mice | 66 |
| Gemfibrozil | Agonist | PPARα | Transcription factor | $T_H2$ cells | N/A | 82 |
| GW-0742 | Agonist | PPARβ/δ | Transcription factor | N/A | EAE | 83 |
| Bexarotene | Agonist | RXR | Transcription factor | $iT_{reg}$ cells | N/A | 65 |
| Clinical trials | | | | | | |
| Statin | Anabolism | HMGCR | Synthesis of mevalonate | N/A | Dyslipidemia[92] | |
| PF-05221304 | Anabolism | ACC1 | Synthesis of FAs | N/A | NASH, NAFLD | 91 |

$iT_{reg}$, *in vitro*-derived $T_{reg}$; N/A: not applicable; NAFLD, nonalcoholic fatty liver disease.