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REVIEW
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Fatty Acid Metabolism and T Cells in Multiple Sclerosis

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Cellular metabolic remodeling is intrinsically linked to the development, activation, differentiation, function, and survival of T cells. T cells transition from a catabolic, naïve state to an anabolic effector state upon T cell activation. Subsequently, specialization of T cells into T helper (Th) subsets, including regulatory T cells (T_{reg}), requires fine-tuning of metabolic programs that better support and optimize T cell functions for that particular environment. Increasingly, studies have shown that changes in nutrient availability at both the cellular and organismal level during disease states can alter T cell function, highlighting the importance of better characterizing metabolic-immune axes in both physiological and disease settings. In support of these data, a growing body of evidence is emerging that shows specific lipid species are capable of altering the inflammatory functional phenotypes of T cells. In this review we summarize the metabolic programs shown to support naïve and effector T cells, and those driving Th subsets. We then discuss changes to lipid profiles in patients with multiple sclerosis, and focus on how the presence of specific lipid species can alter cellular metabolism and function of T cells.

Keywords: T cell, multiple sclerosis, immunometabolism, fatty acids, T regulatory (Treg) cell

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INTRODUCTION

During the course of an immune response, $CD4^+$ T cells transition from a naïve state, participating in immune surveillance, to a highly specialized subset of effector T cells (T_{eff}) equipped with the capacity to rid hosts of invading pathogens and regulate immune responses. As this transition occurs, there is concurrent cellular metabolic remodeling that is intrinsically linked to the development, activation, differentiation, function, and survival of T cells. In addition to the different metabolic requirements of naïve and effector T cells, there are additional metabolic dependencies for $CD4^+$ T helper (Th) subsets and regulatory T cells (T_{regs}), the latter relying on a

Abbreviations: ACC1, Acetyl-CoA carboxylase-1; ATP, Adenosine triphosphate; AMPK, AMP activated protein kinase; CNS, Central nervous system; CSF, Cerebrospinal fluid; DHA, Docosahexaenoic acid; T_{eff}, Effector T cells; EPA, Eicosapentaenoic acid; ETC, Electron transport chain; EAE, Experimental autoimmune encephalomyelitis; FAO, Fatty acid oxidation; T_{fh}, Follicular T helper cells; FFA, Free fatty acid; GM-CSF, Granulocyte macrophage colony-stimulating factor; LCFA, Long chain fatty acids; IFN-γ, Interferon gamma; IL, Interleukin; LDHA, Lactate dehydrogenase; mTOR, Mammalian target of rapamycin; MCFA, Medium chain fatty acids; MS, Multiple sclerosis; OXPHOS, Oxidative phosphorylation; pT_{reg}, Peripheral T_{reg}; PPAR, Peroxisome proliferator-activated receptor; PTEN, Phosphatase and tensin homolog; PI3K, Phosphatidylinositol 3-kinase; PDK1, Pyruvate dehydrogenase kinase 1; Rheb, Ras homologue enriched in brain; Rictor, Rapamycin-insensitive companion of TOR; T_{reg}, Regulatory T cells; SCFA, Short chain fatty acids; TCR, T cell receptor; Th, T helper; tT_{reg}, Thymic T_{reg}; TGF, Transforming growth factor; TCA, Tricarboxylic acid.

different metabolic program than their effector counterparts, displaying metabolic flexibility while maintaining suppressive functions. For example, memory $CD8^+$ T cells use fatty acids derived from extracellular glucose or those mobilized from lysosomes to support their fatty acid oxidation (FAO), whereas T_{regs} acquire fatty acids from the extracellular environment, although the mechanism is not well understood (1).

At the cellular and organismal level, previous studies have shown that nutrient availability in physiological health and disease states can alter T cell function. For example, fluctuations in salt intake and lipid composition in the diet have been shown to change the inflammatory profile of T cells (2–4), and feeding mice diets containing different fatty acid species alter the ratios of T cell subsets and outcome of experimental autoimmune encephalomyelitis (EAE) (5). Additionally, at the cellular level, manipulating metabolic pathways in T cells skews their differentiation towards specific Th cell subsets. Depending on the specific context this can be harmful or beneficial, as metabolic manipulation often determines Th17 versus T_{reg} cell fates (6, 7). Together, the importance of the metabolic-immune axis is critical. However, while the link between metabolism and T cell function is appreciated, specifically how fluctuations in lipid availability, lipid species, and lipid metabolism dictates T cell functions and phenotypes is not well investigated. Studies have also shown that there are changes to lipid profiles in inflammatory settings such as obesity and autoimmune diseases like multiple sclerosis (MS) (8–10), further highlighting the importance of teasing apart the intricate links between metabolic and transcriptional changes within T cells.

In this review we discuss the changes in metabolic states as T cells change from naïve to effector cells and discuss the metabolic requirements driving $CD4^+$ T cell subsets, including T_{reg} cells. We briefly highlight the key roles of T cells in the pathogenesis of multiple sclerosis, and detail findings of altered lipid profiles in MS and murine models of EAE. We highlight data showing that altering lipid metabolism in T cells can alter T cell function in MS and EAE. Finally, we summarize how lipids are trafficked in the body and provide evidence supporting the idea that specific lipid species are capable of altering T cell phenotypes and functions.

IMMUNOMETABOLISM OF T CELLS

Metabolic Remodeling of T Cells Upon Activation

Upon activation, quiescent, naïve T cells have an increased need for cellular energy in the form of adenosine triphosphate (ATP) and biomass to meet proliferative demands and production of effector molecules. As such, the rapidly dividing cells utilize aerobic glycolysis, by which pyruvate is used to produce lactate in the presence of oxygen by cells with a great enough mitochondrial capacity to perform oxidative phosphorylation (OXPHOS), known as the Warburg effect (11, 12). T cell receptor (TCR) signals induce c-Myc, which initiates the expression of metabolic genes to induce glycolysis and mitochondrial metabolism necessary for T cell activation (13, 14). Both c-Myc and mammalian target of rapamycin (mTOR) are positive regulators of glycolysis in T cells (13, 15). mTOR exists as two complexes, mTORC1 and mTORC2. mTORC1 enhances glycolytic metabolism and can regulate other metabolic programs such as lipid synthesis and amino acid metabolism (16). mTOR can partially mediate TCR sensitivity (17), and co-stimulatory signals from CD28 have been shown to upregulate glucose utilization in T cells by recruitment of the phosphatidylinositol 3-kinase (PI3K) catalytic subunit p110γ which activates AKT and mTORC1 (18, 19).

AMP-activated protein kinase (AMPK) is another central node controlling metabolic remodeling during T cell activation. It is activated by TCR signaling *via* two different pathways. The first pathway is LKB1-dependent: AMPK can sense the cellular AMP-to-ATP ratio and control the progression of cells to complete activation (20). The second pathway of AMPK activation is calcium-dependent, mediated by activation of calcineurin and downstream kinase CAMKK (21) (**Figure 1**). T cells that lack AMPK are completely dependent on glycolysis and do not re-engage mitochondrial respiration upon glucose depletion (22). This suggests that activation of AMPK in early T cell activation limits mTOR signaling and prevents premature engagement of glycolysis that is associated with the high proliferative demands of clonal expansion (23). In the mitochondria, the tricarboxylic acid (TCA) cycle creates reducing equivalents that are fed into the electron transport chain (ETC) to generate ATP *via* OXPHOS. Substrates are derived from multiple cytosolic and mitochondrial metabolic pathways including glycolysis and the oxidation of amino acids and fatty acids. FAO translocates free fatty acids (FFA) into the mitochondrial matrix to be broken down and produce acetyl-CoA, which enters the TCA. Acetyl-CoA can also act as a substrate for epigenetic modifications, thereby illustrating how metabolism can directly influence gene expression (24). During the first 24-48 hours after T cell activation, T cells are dependent on ATP production from ATP synthase to become fully activated and meet proliferative demands (25). This reliance on ATP is demonstrated by limited T cell activation after knockdown of the ETC complex IV subunit COX10 (26), and by the inhibition of antigen-specific T cell activation upon loss of ETC complex III subunit RISP (27).

Metabolic Requirements of $CD4^+$ T Cell Subsets

After the initial metabolic reprogramming that occurs with T cell activation, T_{eff} cells use glycolysis to proliferate and maintain their effector functions (28–30). However, Th cell subsets are supported by unique metabolic needs. For example, Th1 cells rely on glycolysis and glutaminolysis to support their growth and proliferation (31), and activating naïve $CD4^+$ T cells in a glutamine deficient environment generates $FOXP3^+$ T_{regs} even in the presence of Th1 polarizing cytokines (32). Further, the by-product of glutaminolysis, α-ketoglutarate, might serve as the metabolic determinant in Th1 differentiation by promoting expression of TBET and mTORC1 signaling (32). mTORC1

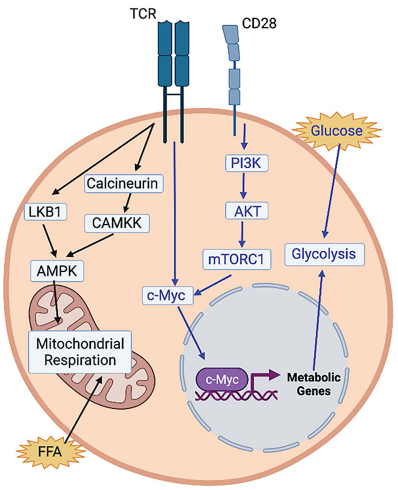

FIGURE 1 | Regulation of T cell activation by metabolic pathways. T cell receptor (TCR) activation activates AMPK via 2 pathways (black arrows). Via an LKB1-dependent pathway and via and LKB1-independent pathway, through calcineurin and CAMKK. Both AMPK and uptake of free fatty acids (FFA) activate mitochondrial respiration, which has been shown to be necessary for T cell activation. Activation of glycolysis is also essential for T cell activation (blue arrows). TCR activation activates c-Myc which turns on the expression of glycolytic metabolic genes. CD28 activation also activates c-Myc via the PI3K-AKT-mTORC1 pathway. Image created with BioRender.com

has been shown to phosphorylate TBET, and inhibition of mTORC1 signaling reduces production of interferon gamma (IFN)-γ (33), highlighting the importance of glucose uptake and aerobic glycolysis in the production of IFN-γ (25, 34, 35). Th1 expression of IFN-γ production is regulated transcriptionally and post-transcriptionally (22, 25), and when activated under glucose-depleted conditions, production of IFN-γ is inhibited (25, 35–38). IFN-γ production is limited by the binding of GAPDH to the 3' UTR of *ifng* mRNA, which is reversed when GAPDH is engaged in glycolysis (25). Epigenetically, glycolysis has been shown to promote IFN-γ production in Th1 cells *via* lactate dehydrogenase (LDHA) (35). LDHA is required to sustain aerobic glycolysis that supports Th1 differentiation, and loss of LDHA leads to reduced H3K9 acetylation at the *ifng* locus that is associated with active transcription and reduced glycolytic flux (35) (**Figure 2**). Moreover, a recent study has demonstrated a role for mitochondrial metabolism in Th1 effector function by showing that mitochondrial metabolism uncouples Th1 proliferation and effector functions. The TCA cycle, and specifically, succinate dehydrogenase activity (ETC complex II), is required for Th1 effector functions including expression of IFN-γ, but suppresses proliferation and histone acetylation. Conversely, complex I of the ETC, the malate-aspartate shuttle, and mitochondrial citrate export maintain Th1 proliferation and promote histone acetylation to regulate T cell activation genes (39).

In correlation with enhanced glycolytic metabolism, *in vitro*-generated Th17 cells express higher levels of pyruvate dehydrogenase kinase 1 (PDK1), which is essential for Th17 differentiation *in vitro* (40, 41). Th17 cells differentiated *in vitro* utilize both OXPHOS and glycolysis, and Th17 cells from steady state and inflamed tissues rely on OXPHOS for cytokine production (40). In support of these data, the OXPHOS inhibitor oligomycin reduces Th17 pro-inflammatory cytokine production and improves pathology in mouse models of colitis (40). Evidence suggests that lipid metabolism plays an important role in the function of Th17 cells under normal and stressed conditions (42, 43), and Th17 cells rely on *de novo* fatty acid synthesis, rather than acquisition of extracellular fatty acids (42). While the reasons for this are unclear, it has been shown that Th17 cells are particularly dependent on cholesterol synthesis, as intermediates of the pathway can bind to the RORγt promoter and promote interleukin (IL)-17 expression, whereas inhibition of cholesterol biosynthesis blocks Th17 development (44, 45). The ratio of intracellular saturated to polyunsaturated fatty acids has been shown to control CD5L expression, which can determine whether or not Th17 cells will adopt a pro- or anti-inflammatory phenotype (46). Saturated to polyunsaturated FFA ratios also affect the expression of metabolic genes *cyp51* and *sc4mol*, which synthesize ligands for RORγt (43, 46). Given the intricacies of Th17 and T_{reg} development, studies are unveiling a role for metabolic intermediates in skewing T cell lineages alongside cytokine polarization. For example, acetyl-CoA carboxylase-1 (ACC1)-deficient T cells default to the T_{reg} lineage (6), and mice fed a high fat diet increases the expression of ACC1 in $CD4^+$ T cells, which upregulates the expression of the Th17 master regulator, RORγt (7) (**Figure 2**). The increase of ACC1 expression in $CD4^+$ T cells is mimicked in obese individuals and proposed to contribute to associated Th17 pathologies (7).

Th2 cells have been reported to display high glycolytic activity (31, 47). Ras homologue enriched in brain (Rheb) is a small GTPase that activates mTORC1. Rheb-deficient mice have impaired mTORC1 function and fail to generate Th1 and Th17 cells without alterations in Th2 differentiation. Conversely, rapamycin-insensitive companion of TOR (Rictor) is a component of the mTORC2 complex, and Rictor-deficient mice have impaired mTORC2 signaling, with differentiation into Th2 cells, but intact Th1 and Th17 generation (48). Further, downstream targets of mTORC2, SGK1 and the GTPase RhoA, have been shown to play important roles in the commitment to, and function of Th2 cells, respectively (49, 50). These data suggest mTORC2 is the signaling determinant of the Th2 lineage, not mTORC1, and that glycolytic engagement differs between Th2 and Th1 and Th17 lineages. Genome-wide transcriptional profiling of human Th2 cells from allergic asthma patients demonstrate a positive correlation between the expression of c-Myc and disease state further supporting glycolysis as a marker of Th2 pathogenicity (51). Lipids might also play a role in Th2 metabolism, as expression of peroxisome proliferator-activated receptor (PPAR)-γ is critical for Th2 responses against house dust mite antigens, and PPARγ-deficient mice display Th2 cells unable to produce IL-5 and IL-13 (51, 52) (**Figure 2**).

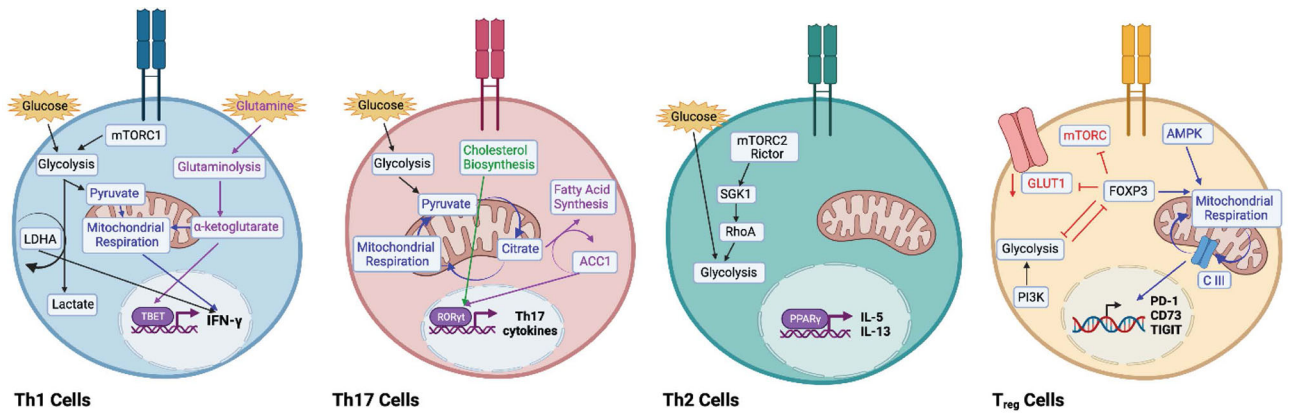

FIGURE 2 | Metabolic remodelling to promote Th helper T cell subsets. Th1 cells engage in glycolysis (black arrows) and aerobic respiration (blue arrows) to support interferon (IFN)-γ expression. Lactate dehydrogenase (LDHA) has been shown to promote IFN-γ expression. Inhibition of mTORC1 decreases IFN-γ expression. Glutaminolysis (purple arrows) via α-ketoglutarate promotes TBET expression. Th17 cells use both glycolysis (black arrows) and oxidative phosphorylation (blue arrows) to secrete Th17-associated cytokines. Acetyl-CoA carboxylase 1 (ACC1) promotes RORγt expression (purple arrows), and intermediates of cholesterol biosynthesis (green arrows) support the RORγt program. Th2 cells are supported by high levels of glycolysis. The mTORC2-Rictor complex supports the Th2 lineage via SGK1 and RhoA (black arrows). Peroxisome proliferator- activated receptor (PPAR)-γ has been shown to promote IL-5 and IL-13. Regulatory T (T_{reg}) cells are supported by mitochondrial respiration (blue arrows), as AMPK expression drives fatty acid oxidation and oxidative phosphorylation. Complex III of the electron transport chain supports the expression of immunosuppressive genes like PD-1, CD73, and TIGIT. Expression of FOXP3 promotes AMPK expression and inhibits expression of mTORC1, GLUT1, and glycolysis (red arrows). Activation of PI3K drives glycolysis and decreases Treg suppression (black arrows). Glycolysis and FOXP3 reciprocally regulate each other. Image created with BioRender.com

Metabolic Adaptations of Regulatory T Cells

In contrast to T_{eff} cells, T_{regs} appear to exhibit a greater capacity for metabolic flexibility. Murine T_{regs} have been described to preferentially rely on OXPHOS rather than aerobic glycolysis for ATP production (31). However, metabolic adaptations of T_{reg} cells are context-dependent and influenced by T_{reg} origin and anatomical distribution (53). It remains unclear how thymic-derived T_{regs} (tT_{regs}) and T_{regs} differentiated in the periphery from conventional T_{eff} cells, termed peripheral T_{regs} (pT_{regs}) differ metabolically. However, it appears that T_{reg} proliferation and effector functions are maintained through different metabolic programs. Proteomic analysis of human T_{reg} and T_{eff} cells suggests that freshly isolated T_{regs} are highly glycolytic and proliferative, while *in vitro* proliferating T_{regs} engage in both glycolysis and FAO (53). Conversely, T_{eff} cells switch from OXPHOS to aerobic glycolysis upon *in vitro* activation, and FAO appears to be indispensable for proliferation and effector functions (53). One explanation for the discrepancy between human and murine models is that mice are typically housed in pathogen-free environments, whereas human immune cells are constantly engaging with pathogens that requires T_{regs} to meet higher proliferative and functional demands (54).

AMPK and mTORC1 signals are important determinants of T_{reg} fitness. T_{reg}-specific mTOR deletion impairs T_{reg} fitness and homeostasis resulting in a reduction of T_{regs} in the tissues and T_{eff} cell activation and heightened inflammation at barrier sites (55). Inhibiting mTORC1 by rapamycin along with IL-2 signaling greatly expands T_{reg} numbers (56). Conversely, AMPK, which activates FAO and OXPHOS, provides critical signals required for T_{reg} differentiation (57). Activation of AMPK by metformin induces T_{reg} differentiation and, in murine models, was sufficient to limit progression of EAE and inflammatory bowel disease (31, 58, 59).

FOXP3 is involved in the fine tuning of metabolic cues to maintain T_{reg} function. Inflammatory stimuli and FOXP3 oppose each other through regulation of mTORC1 and glucose metabolism as T_{reg} treatment with TLR1/TLR2 agonists enhances mTORC1 activity and T_{reg} proliferation but reduces their suppressive capacity (60). In contrast, FOXP3 inhibits mTORC1 signaling and glycolysis while promoting OXPHOS and reduces the rate of proliferation (60), suggesting that mTORC1 activity and glycolysis are adequate for T_{reg} proliferation in inflammatory environments. However, excessive mTORC1 activity impairs T_{reg} function and indeed T_{regs} suppress mTORC1 activity *via* PP2A (48, 61, 62). Murine T_{regs} induced *via* transforming growth factor (TGF)-β express low levels of GLUT1 compared to T_{eff} cells (31), and in human T_{regs}, GLUT1 expression is also thought to be limited by FOXP3 *via* AKT inhibition (63). T_{regs} that overexpress GLUT1 exhibit reduced CD25 and FOXP3 expression and fail to suppress colitis (60). Expression of FOXP3 allows T_{regs} to survive in lactate rich environments by increasing the ratio of NAD to NADH (64). T_{reg} proliferation and suppressive functions can be uncoupled metabolically, which is likely advantageous in an inflammatory setting. For example, it might be advantageous for T_{regs} to engage in glycolysis to rapidly proliferate and deprive proliferating T_{eff} cells of an essential nutrients, then switch to an OXPHOS

program for optimal suppressor functions. Of note, PI3K-mTORC2 mediated activation of glucokinase, which activates glycolysis and mediates actin cytoskeletal rearrangements, was found to be important for proper migration of T_{regs} in skin allograft models (65). Therefore, although glycolysis seems to play a role in T_{reg} migration and proliferation, utilization of OXPHOS appears to be the main metabolic program utilized for T_{reg} function, which is dependent on FAO (31).

Cytokines that promote T_{reg} differentiation such as TGF-β (66), activate AMPK (67) and promote FAO to skew naïve T cells into a T_{reg} phenotype instead of pro-inflammatory Th17 cells (31, 68). In support of this observation, T_{reg} differentiation and suppressive functions are reduced by the FAO inhibitor etomoxir (31), and suppression of PI3K activity by phosphatase and tensin homolog (PTEN) drives T_{reg} differentiation (69). PTEN-deficient T_{regs} have elevated glycolytic activity and lose FOXP3 expression and suppressive function (70). These data suggest that the balance between PTEN and AKT functions can regulate T_{reg} differentiation. Data also suggest a reciprocal relationship between FOXP3 and glycolysis as FOXP3 has been shown to interfere with c-Myc expression to dampen glycolytic activity (64) and forced expression of FOXP3 suppresses glycolysis-related genes while inducing lipid and oxidative metabolic genes required for maximum suppression (60). In murine models, mitochondrial complex III is required for T_{reg} suppression through the active metabolism of 2-HG and succinate, resulting in de-repressed transcription of T_{reg} suppressive genes, including PD-1, CD73, and TIGIT (**Figure 2**). Moreover, loss of mitochondrial complex III function accumulates 2-HG and succinate, which inhibits demethylases and represses transcription of T_{reg} suppressive genes PD-1, CD73, Nrp1, and TIGIT. In addition, mice containing a RISP knockout, an essential component of mitochondrial complex III, die after one month exhibiting lethal inflammation as characterized by enlargement of lymph nodes and spleens along with lymphocytic infiltration into multiple organs (71).

Interestingly, in human T_{regs}, glycolytic activity has been linked to suppressive function *via* enolase-1, which mediates expression of a specific splice variant of FOXP3 that is necessary for suppression (72). However, this study also showed that the relationship between FOXP3 and metabolic intermediates changes depending on which metabolic program the cells are engaging. Upon inhibition of glycolysis with 2-DG, the non-glycolytic activity of enolase-1 represses FOXP3 expression, whereas the generation of T_{regs} under suboptimal TCR stimulation promotes FOXP3 expression *via* the glycolytic activity of enolase-1 (72) (**Figure 2**). Lack of mTOR activity does not decrease FOXP3 expression, but it does diminish cholesterol biosynthesis that has been shown to be required for suppressive function *in vivo* (73). Therefore, T_{regs} seem to be partially dependent on mTOR and glycolytic signals that are more oscillatory in nature (74), or perhaps for maintenance of metabolic intermediates that feed into lipid related pathways, as seen with cholesterol.

Fatty acids can induce cell death in T cells (75–78). It is suggested that T_{regs} have specifically evolved FAO dependence to combat fatty-acid-induced cell death *via* FOXP3 (79). For example, long chain fatty acids like palmitate, are pro-apoptotic through various mechanisms, including depolarization of mitochondrial action potential and reactive oxygen species generation (80). This shows that FOXP3 uniquely enables T_{regs} to utilize fatty acids as fuel by upregulating enzymes to engage in FAO and become resistant to apoptosis (79). This evolved anti-apoptotic strategy is likely even more useful during steady state or inflammation as T_{regs} are important in the maintenance of homeostasis in lipid-rich tissue environments. Undoubtedly, the metabolic-functional axis in these cells is incredibly complex, and is essential to our complete understanding of disease pathology and resolution.

Overall, it is clear that T cell metabolic programs are flexible and highly dynamic. T cells can utilize different substrates based on metabolic needs, and tailor metabolic programs to support effector functions. Studies investigating Th-subset differentiation show that specific metabolic engagements promote and suppress specific Th-lineage differentiation and functions.

THE ROLE OF LIPIDS IN T CELL FUNCTION

Introduction to Lipids and Lipid Trafficking

Lipids provide the foundation of both cellular and organelle membranes, serve as fuel for cells, and are the precursors of bioactive lipid mediators. Lipids are incredibly diverse, just like proteins; however, because of limitations in technologies to study lipids, we are just beginning to understand the diverse effects lipids exert on biological processes such as gene expression and cellular function. It is understood that the storage and secretion of lipids from the adipose tissue is one mechanism by which the body can communicate hunger and the need for energy (81, 82). However, during lipolysis and even inflammation, FFAs are exposed to immune cells that reside in the tissues and in circulation. How immune cells sense and interpret these signals remains an active area of research, as evidence is emerging that not all lipids are created equal and perform the same functions on specific cell types.

Cells obtain fatty acids from lipid species in the diet, fats stored in cells as lipid droplets, and lipids synthesized in one organ for export to another. Lipid species from the diet are ingested as triglycerides, which travel into the small intestine where they are emulsified by bile salts, and form hydrophobic structures called micelles. Together, bile salts and pancreatic lipases breakdown triglycerides into FFAs. FFAs in the intestine are transported across intestinal cell membranes, where they are converted back into triglycerides, and packaged with cholesterol and other apolipoproteins into vesicles called chylomicrons. Chylomicrons move freely from the intestines, through the lymphatic system, and into the bloodstream where they either

enter the liver, or the adipose tissue. In the adipose, they will either be oxidized for fuel, or stored until they are needed. When hormones in the body signal the need for metabolic fuel, triglycerides that are stored in adipose tissue are mobilized and transported to other tissues throughout the body where the fatty acids may be oxidized for energy (81).

Similar to amino acids, there are both essential and non-essential fatty acids. Essential fatty acids comprise groups of lipids that must be acquired from the diet, as they cannot be synthesized in the body. These include omega-3 and omega-6 fatty acids. Omega-3 fats are derived from fish, eggs, and other plant based sources and are typically associated with anti-inflammatory effects (82). In contrast, omega-6 fatty acids are found various oils and animal meats and are associated with the production of inflammatory bioactive mediators (83). Of interest, these two groups of fatty acids can compete with each other for insertion into cellular membranes, where they are cleaved and converted into lipid mediators and other signaling molecules (84). Further, studies have shown due to this competition, fats in the diet reflect the overall lipid composition in cellular membranes (84–87), highlighting an important link between diet and inflammatory status. Therefore, fat sources enriched in the Westernized diet may partially explain rises in some inflammatory associated diseases.

FFAs are further characterized according to length and saturation. SCFA are typically classified as having fewer than six carbons, whereas medium chain fatty acids (MCFA) contain between six to twelve carbons, and LCFA are those with more than twelve carbons. Saturated fatty acids contain no double bonds in their carbon tail, whereas monounsaturated and polyunsaturated fatty acids contain one double bond, and more than one double bond, respectively. SCFAs are able to freely move into the mitochondria for β-oxidation, whereas LCFAs must first enter the carnitine shuttle. Of note, the majority of FFAs obtained from the diet or released from the adipose tissue are MCFA or LCFAs. On the other hand, most of the SCFA studied are those derived from bacterial metabolism and associated byproducts.

Lipids Altering Immune Cell Phenotypes

There is great focus on understanding factors that drive and regulate immune cell phenotypes and functions in tissues. Recent studies have described contributions from cytokines and hormones secreted from tissue-resident cells and other neighboring immune cells (88–91), the presence of local antigens driving immune cell persistence in the tissues (88, 92, 93), and the changes in nutrients that prompt metabolic reprogramming in specific microenvironments, such as tumors (94, 95). Evidence has shown that $CD4^+$ T cell fate is driven by availability of metabolic substrates and cell-intrinsic programs that determine metabolic requirements (96). Metabolic reprogramming is critical for T cell proliferation, differentiation, and function, however, how specific substrates such as lipids, affect T cells remains unanswered. T_{regs} rely mainly on FAO-driven OXPHOS for survival and function (31), so lipid species in the tissues likely provide a critical signal for maintenance of T_{reg} survival and homeostatic functions within tissues as well. It is likely that altered lipid profiles in disease settings can impact T cell function and is of great interest to fully understand how tissue microenvironments shape T cell metabolism.

Recent data have shown that the length of fatty acids can differentially affect immune cell phenotypes. In the colon, resident gut bacteria produce SCFAs as a byproduct of fermentation (97, 98), which shapes the colonic T_{reg} population (99). The addition of the SCFA propionate to the drinking water of germ-free mice increases T_{reg} numbers in the colon, but not spleen or thymic T_{reg} numbers. Further, antibiotic-mediated depletion of gut bacteria reduces T_{reg} numbers that can be rescued with the addition of propionate to the drinking water (99). SCFAs promote FOXP3 expression and are dependent on fatty acid receptor, GPR43 (100, 101). In support of these data, the addition of SCFAs to naïve $CD4^+$ T cells increases the proportion of $FOXP3^+$ cells upon activation. However, the addition of LCFAs results in $CD4^+$ T cells that produce more pro-inflammatory cytokines including IFN-γ and IL-17a that exacerbate EAE (5).

Unsaturated fatty acids like oleic acid and linoleic acid have been shown to modulate cytokine production in T cells (102, 103), but only saturated fatty acids induce cytokine secretion in the absence of T cell activation in a dose-dependent manner (102). In T cells, oleic acid has been shown to induce proliferation in the spleen and lymph nodes, but to inhibit Jurkat cell proliferation and IL-2 and IFN-γ production (104). In $CD4^+$ T cells, fatty acid synthesis blockade by the inhibitor TOFA, reduces proliferation, which can be rescued by the addition of oleic acid specifically (105). Moreover, oleic acid can also rescue proliferation of $CD4^+$ T cells cultured in fatty acid-free media (105). Interestingly, oleic acid has also been shown to decrease the content of arachidonic acid in cell membranes that result in decreased arachidonic acid-derived pro-inflammatory lipid mediators (86, 87), and to inhibit palmitic-induced inflammation in type 2 diabetes (106). Mechanistically, attenuation of palmitic acid-induced inflammation by oleic acid is linked to increases in CPT1a expression and FAO driven by AMPK activation. In adipocytes, oleic acid induces IL-10 and adiponectin expression which can activate AMPK (106). We have also shown that oleic acid is one of the most prevalent fatty acids in human adipose tissue, and is significantly decreased in the adipose tissue from MS patients (4).

In EAE models, docosahexaenoic acid (DHA) downregulates Th1 and Th17-related cytokines (107). Both DHA and eicosapentaenoic acid (EPA) have been shown to modulate the JAK-STAT pathway and IL-2 signaling in T cells (108). In Jurkat cell lines DHA exerts immunosuppressive effects by increasing calcium concentrations in cells (109–111). Similarly *in vivo*, mice fed a DHA- and EPA-enriched diet exhibited reduced T cell proliferation and IL-2 signaling (77, 112, 113). DHA has been also shown to induce dose-dependent reductions in the ability of T_{regs} to inhibit effector T cell proliferation. In contrast, DHA can upregulate FOXP3 mRNA and other immunosuppressive cytokines such as IL-10 (114).

Saturated fatty acids like palmitic acid have been shown to drive T cell activation *via* the PI3K/AKT pathway (5, 115, 116). Palmitic acid treatment also induces the expression of cytokines related to T cell activation such as IL-2, IL-6, IL-17A, TNF-α, and IFN-γ (102, 116). Similarly, lauric acid has been shown to have some pro-inflammatory properties, as it increases IL-2 and can promote Th17 differentiation in models of EAE (117).

The PPAR family of lipid receptors has been implicated in T cell biology, through regulation of IL-2 production (118–120), influencing Th17 and T_{reg} differentiation (121), and regulation of inflammation (121–126). Similarly, SREBPs are transcription factors that regulate gene expression related to lipogenesis and cholesterol synthesis and uptake (127). SREBPs are important for lipid membrane synthesis that allows rapid expansion of proliferating T cells (128). However, in the absence of fatty acids or upon blockade of FAO, T_{reg} development is inhibited *in vitro*. T_{regs} rely on exogenous fatty acids as their metabolic substrate (31, 42), which seems to impart a survival advantage for T_{regs} as FOXP3 alone upregulates enzymes associated with FAO and OXPHOS (79). Interestingly, triglyceride storage in T_{regs} limits protein kinase C activity to promote FOXP3 expression, potentially highlighting a feedback mechanism between exogenous fatty acid uptake in T_{regs} (79). Much of these data support the idea that fatty acids can differentially effect T_{eff} cells and T_{reg} subsets, but further, that specific fatty acid species have the potential to differentially affect T_{reg} biology. However, the mechanism driving these changes remains unknown.

T CELLS IN MULTIPLE SCLEROSIS

MS is an autoimmune disorder characterized by aberrant immune responses and immune cell infiltration in the central nervous system (CNS). Both relapsing-remitting MS and progressive MS experience demyelination and neurodegeneration because of ongoing inflammation in the CNS (129–131). Multiple immune cell types are found in the MS brain; however, autoreactive T cells are considered the main mediators of inflammation (132–137). In particular, the $CD4^+$ T cell subsets, Th1 and Th17 cells promote inflammation *via* interactions with other immune cells types, such as B cells, follicular T helper cells (T_{fh}) cells, and resident CNS microglia. T_{fh} cells support B cell survival, differentiation, and expansion *via* interactions in the germinal center and through secretion of cytokines like IL-21 (138, 139). T_{fh} cells have been reported in MS lesions (140). In addition, numerous markers of T_{fh} cells, such as IL-21, are upregulated in MS (141), and altered ratios of T_{fh} cells have been reported (142). For instance, MS patients have elevated ratios of Th17-like T_{fh} cells, which are considered pathogenic and support B cell antibody production (142). Thus, T_{fh} cells likely play an important role in MS pathogenesis by supporting autoreactive B cell antibody production.

Th1 $CD4^+$ T cells that are associated with MS express the transcription factor TBET and secrete pro-inflammatory cytokines IFN-γ and TNF-α, whereas Th17 associated $CD4^+$ T cells express RORC2 and secrete IL-17, IL-21, and IL-22 cytokines. Both IFN-γ and IL-17 are thought to enhance immune activation and have been strongly associated in human disease, as the frequencies of Th1 and Th17 cells are increased in MS lesions and the cerebrospinal fluid (CSF) (130, 143). However, there is a dichotomous nature to the roles of Th1 and Th17 cells in MS. Increases in Th17 cells have been measured during clinical relapse in the CSF of MS patients (143); whereas other studies have found increases in IFN-γ upon relapse (144). Despite these differences, evidence suggests that both IFN-γ and IL-17 are pathogenic in MS, however, different cytokines might play different roles depending on the stage of the disease (for example initiating events of the disease versus exacerbation of the disease). Furthermore, with advances in single cell technologies, there is growing evidence of subsets within Th cell subsets, so it is likely that not all IFN-γ or IL-17-producing cells are pathogenic, but perhaps only a subset of these cells, making the signals and environmental cues that drive these pathogenic subsets of great interest to define.

Of importance are the pathogenic Th17 cells that secrete both IFN-γ and IL-17 and express both TBET and RORγt, termed Th1-like Th17 cells, which are found in multiple autoimmune disorders like multiple sclerosis (145), insulin-dependent diabetes mellitus, autoimmune arthritis and inflammatory colitis (146, 147). In EAE, Th1-like Th17 cells have been found to be the main drivers of disease pathology (148), and in humans, $IFN\text{-}\gamma^+$;$IL\text{-}17^+$ T cells are found in the blood and brain tissue of MS patients (149). These Th1-like Th17 cells are capable of crossing the blood brain barrier and have been correlated with inflammation in both MS patients and EAE models (148–150). Th1-like Th17 cells can also secrete granulocyte macrophage colony-stimulating factor (GM-CSF) which augments inflammation by activation of innate immune cell populations (151, 152). In contrast, subsets of Th17 cells can produce IL-10 and thought to play a more suppressive, protective role in inflammatory settings (153–156).

Another consequence of the ongoing inflammation in MS are the functional changes that occur in T_{regs}. Under homeostatic conditions T_{regs} are responsible for the maintenance of immune tolerance by preventing aberrant or excessive immune responses. However, during chronic inflammation, as with MS, T_{regs} acquire effector like properties, and express IFN-γ, termed, Th1-like T_{regs} (157). Th1-like T_{regs} upregulate other Th1 markers, such as TBET and CXCR3, and are less suppressive than their control counterparts *in vitro* (157). Increased frequencies of Th1-like T_{regs} have been found in patients with MS, type 1 diabetes, and in mouse models of Sjögren Syndrome, and are thought to contribute to the loss of tolerance in autoimmune diseases (158). Th1-like T_{regs} secrete IFN-γ *via* activation of the PI3K-AKT-FOXO1/3 pathway, and using an *in vitro* approach, activation of PI3K has been shown to be sufficient to induce a Th1-like phenotype in human T_{regs} (159, 160). Given that mTORC1 is downstream of the PI3K pathway it is possible that alterations in cellular metabolism also accompany such examples of T_{reg} plasticity.

Development of MS is thought to arise from unfavorable interactions between genetic risk loci and environmental conditions and/or cues. Numerous environmental triggers have

been proposed, including smoking, vitamin D, EBV infection, salt, and gut microbiota (161, 162). However, none of these factors reconcile the rise in MS incidence in the western world, except the changes in diet and consequential rise in obesity. The Western diet contains greater concentrations of salt, refined sugars, and unsaturated fats (163). We have reported that the physiologic sodium concentrations induce an inflammatory signature in T_{eff} cells and drives a Th1-like phenotype in T_{regs} (2). Further, obesity has been identified as another risk factor for the development of MS, and adipose tissue of obese patients has been shown to host a chronic, pro-inflammatory environment, indicating that diet can influence immune cell activation and phenotypes within tissues, which might play an important role in MS (164, 165).

Altered Lipid Profiles in Multiple Sclerosis

Lipids play many roles in the CNS including signaling, structural support, mediating inflammation, and membrane biogenesis (9). Therefore, during inflammation changes in the availability and profiles of FFA species might alter disease pathogenesis by influencing immune cell function. In multiple sclerosis, immune cells attack the myelin sheath around nerves that are rich in lipids, containing approximately 700 different lipid species (11, 15, 16), and as a result many studies have found altered lipid profiles in the MS patients and EAE models (8, 166), that could potentially serve as biomarkers of the disease. At the time of diagnosis, the CSF of MS patients harbor differences in many lipid species, including pro-inflammatory arachidonic acid, compared to the non-MS control group (167). In support of these data, lipid profiling of mouse EAE brains showed that during acute inflammation, lipid metabolism is shifted from the pathway that creates common lipid substrates into the pathway producing the pro-inflammatory arachidonic acid (168). Studies profiling the phospholipids of serum samples from patients with MS have also demonstrated that patients with MS have a phospholipidomic signature different from that of healthy controls (169).

Altered T Cell Metabolic Profiles in Multiple Sclerosis

As with infections and metabolic syndromes, the inflammation induced in autoimmunity triggers metabolic alterations locally and systemically (166). In the blood of patients with MS and other autoimmune disorders such as rheumatoid arthritis and systemic lupus erythematosus, there are elevated levels of IL-1β, IL-6, TGF-β, and IL-23, which promote pathogenic Th17 cell differentiation and block T_{reg} development *in vivo* and *in vitro* (170–176), proving that there is a disturbance in the balance between the induction and regulation of pro-inflammatory T_{eff} cells. Although the metabolic cues that shift this balance are still being defined, there is evidence that glycolysis and OXPHOS are impaired during T cell activation in relapsing-remitting MS patients (177).

As mentioned above, glycolysis is a common feature of Th1 and Th17 $CD4^+$ T_{eff} cells (13, 47). Inhibiting glucose metabolism can inhibit differentiation of Th1 and Th17 lineages even in the presence of polarizing cytokine (31, 47). Further, blocking glycolysis using 2-deoxyglucose (2-DG) improves clinical outcomes in EAE models (47) (**Figure 3**). A direct link between dysregulated glucose metabolism in lymphocytes and autoimmunity was shown in mice that over-express GLUT1 in T cells (178). Increased glucose uptake drives IFN-γ and IL-2 expression in T cells upon *in vitro* stimulation, and deletion of *GLUT1* reduces glycolysis in $CD4^+$ T cells, and effector differentiation. These cells are also unable to provide protection in a model of colitis (34). Further, $CD4^+$ T cells in lupus-prone mice show increases in glycolytic engagement compared to healthy control cells (179).

Some studies have reported alterations in T cell lipid metabolism as a contributor to MS pathogenesis (180–183). Activated T cells have higher cholesterol and fatty acid concentrations in their membrane (184, 185), therefore altered lipid-mediated signaling could contribute to MS pathogenesis (186). Specific deletion of ACC1 in T cells protects mice from EAE by reducing the number of IFN-γ^+ Th17 cells and increases the number of $FOXP3^+$ T_{regs} in the spinal cord (42). Conditional deletion of LDHA in T cells protects susceptible mice from Th1-mediated autoimmunity (35). Simvastatin, an inhibitor of cholesterol biosynthesis, was used in a clinical trial to treat MS and was able to attenuate brain atrophy and disease progression (187). In support, during the chronic phase of EAE, linoleic and cholesterol metabolism have been found to be altered (9, 10), and inhibition of cholesterol synthesis *via* statins, prevented EAE progression by blocking Th17 differentiation (188). However, statins broadly affect the immune system, including promotion of Th2 cells and inhibition of the cytokines that induce Th1 and Th17 differentiation, and therefore their effect on MS might not be directly related to their effect on cholesterol (187–189).

Long chain fatty acids (LCFAs) and short chain fatty acids (SCFAs) have been shown to exert opposing effects on T cell differentiation. LCFAs promote IFN-γ and IL-17 production and exacerbate EAE, whereas SCFAs induce FOXP3 expression and provide protection (5). We have recently shown that T_{regs} isolated from the adipose tissue of MS patients exhibit a pro-inflammatory transcriptome that resembles the transcriptome of T_{regs} treated *in vitro* with the pro-inflammatory LCFA arachidonic acid (4). T_{regs} isolated from the adipose of healthy subjects and T_{regs} exposed to oleic acid *in vitro* do not show an inflammatory transcriptome, but rather exhibit increased FAO-driven OXPHOS metabolism, creating a positive feedback mechanism that induces the expression of FOXP3 and enhances phosphorylation of STAT5, which acts to stabilize the T_{reg} lineage and increase suppressive function (4). Finally, treating dysfunctional MS T_{regs} with oleic acid can partially restore their suppressive function, highlighting a role for dietary lipids in shaping T_{reg} function and identity in MS (4, 92, 190, 191) (**Figure 3**). Further studies must address how metabolic perturbations generate and sustain pathogenic T cells in the context of MS and other autoimmune diseases. Metabolic signatures of T cells are intricately linked to their differentiation and activation status. However, under inflammatory conditions such as infection or during metabolic syndromes, autoimmunity,

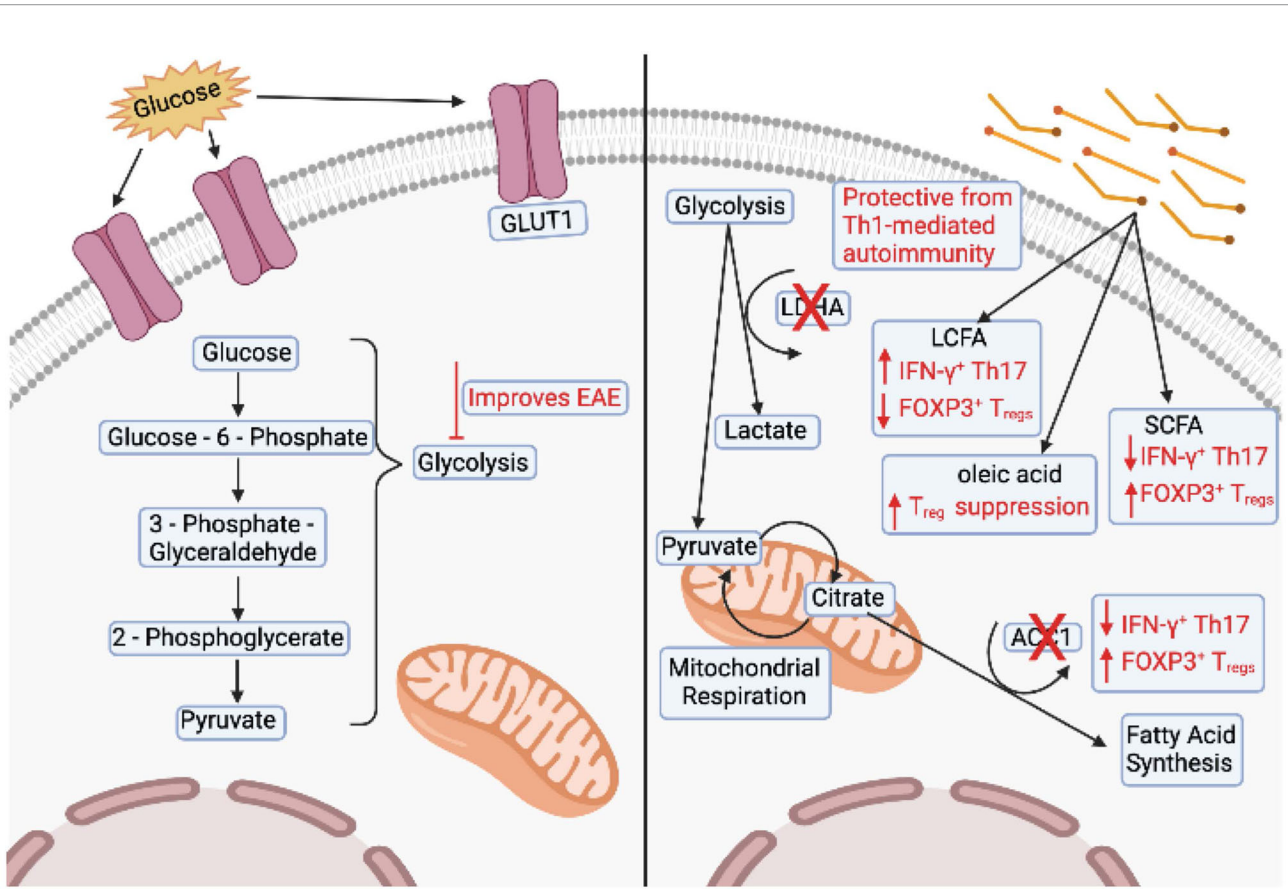

FIGURE 3 | Changes in T cells associated with multiple sclerosis. The left panel shows overexpression of GLUT1 and dysregulation of glycolysis associated with T cells in experimental autoimmune encephalomyelitis (EAE) models. Inhibition of glycolysis also improves clinical outcomes of EAE. The right panel shows that deletion of lactate dehydrogenase (LDHA) is protective in Th1-mediated autoimmunity. Deletion of acetyl-CoA carboxylase 1 (ACC1) in T cells decreases the number of interferon (IFN)-γ+ Th17 cells and increases the number of FOXP3+ Treg cells. Mice fed long chain fatty acids (LCFAs) have an increased number of IFN-γ+ and IL-17+ T cells and a decreased number of FOXP3+ cells. Conversely, mice fed short chain fatty acids (SCFAs) have an decreased number of IFN-γ+ and IL-17+ T cells and an increased number of FOXP3+ cells. Finally, T cells cultured in the presence of LCFA, oleic acid, can partially restore Treg suppression. Image created with BioRender.com

and cancer, the microenvironment drastically changes in regard to nutritional availability, forcing T cells to adapt to these changing environments.

Future studies focusing on how nutrient depletion or metabolite availability shapes metabolic utilization and differentiation of T_{eff} and T_{reg} cells will be critical to our understanding and implementation of targeted therapies. For example, Shi et al. have shown that blocking glycolysis improves clinical outcomes of EAE (47), and disease-modulatory effects of feeding mice both LCFAs and SCFAs have been observed (5). However, to realistically translate these data to human therapies we must first develop more reliable metabolic profiles of T cells and other cells involved in disease pathogenesis and progression during active disease states. Once established, we can couple these data to cytokine profiles or other functional readouts, e.g. suppressive capacity of T_{regs}, in order to more precisely define relevant metabolic targets. One current limitation of metabolic therapies is that the target molecules are often the regulators of central metabolic nodes that integrate many signals and crosstalk between multiple pathways, such as mTOR. However, the ability to fine tune T cell functions and phenotypes that are more favorable for disease outcomes will depend on specifically targeting certain metabolic intermediates.

CONCLUSIONS

Lipids are a critical component of all cellular and organelle membranes. They provide structural support to the cell, serve as fuel, and signaling platforms. Lipid species are as diverse as proteins, however, limitations in technologies to study lipids

have left major gaps in our understanding of their range of impacting biological functions, especially in lymphocytes. Despite these gaps, we know that different T cell subsets differentially utilize lipids for fuel and function (192). Upon activation of an T_{eff} cell, there is a switch from a predominantly OXPHOS metabolic program to aerobic glycolysis, a more anabolic process critical for growth and proliferation during an immune response (47, 192). Conversely, OXPHOS mainly supports survival of T_{regs} and memory T cells (31). Although these cell types rely on the same metabolic program, they acquire and utilize lipid species differently (15). Given the diversity of FFAs, profiling lipid composition in tissues is crucial to understand which FFA species might be important in regulating T cell function in specific microenvironments and physiological states. Current data show the pleiotropic effects lipid species exert on T cells, depending on fatty acid length, degree of saturation, and nutrient availability in the environment. There are clear correlations and fluctuations in lipid profiles with diet and disease states, so understanding these differences will be critical to discern how lipid signaling and lipid-driven metabolism affects the function and phenotypes of T cells in disease states. There are many remaining questions regarding fatty acid-specific effects on T cell function. For example, it is not well defined which FFA are preferentially metabolized, which can serve as signaling molecules, or which FFA exert their effects by increasing intermediates generated by FAO or other downstream metabolic processes. It is also not fully understood if lipid receptors display degrees of specificity beyond FFA length. Better characterization of these receptor families could potentially provide insight as to which FFA are being utilized by T cell subsets and how the receptor expression profile might shift in specific disease states. Regardless, given the constant exposure of T cells to lipid species in the tissues, it is certain these molecules have important implications in T cell biology.

AUTHOR CONTRIBUTIONS

SLP wrote the manuscript under the supervision of MD-V and DAH. Correspondence should be addressed to MD-V. All authors contributed to the article and approved the submitted version.

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