frontiers in Immunology

REVIEW
published: 14 March 2022
doi: 10.3389/fimmu.2022.840610

T Cell Metabolism in Infection

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T lymphocytes (T cells) are divided into two functionally different subgroups the CD4+ T helper cells (Th) and the CD8+ cytotoxic T lymphocytes (CTL). Adequate CD4 and CD8 T cell activation to proliferation, clonal expansion and effector function is crucial for efficient clearance of infection by pathogens. Failure to do so may lead to T cell exhaustion. Upon activation by antigen presenting cells, T cells undergo metabolic reprograming that support effector functions. In this review we will discuss how metabolic reprograming dictates functionality during viral infections using severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and human immunodeficiency virus (HIV) as examples. Moreover, we will briefly discuss T cell metabolic programs during bacterial infections exemplified by *Mycobacterium tuberculosis* (MT) infection.

Keywords: T cells, metabolism, immunometabolism, infection, HIV, COVID-19, tuberculosis

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Specialty section:
This article was submitted to T Cell Biology, a section of the journal Frontiers in Immunology

Received: *21 December 2021*
Accepted: *17 February 2022*
Published: *14 March 2022*

Citation:
Wik JA and Skålhegg BS (2022) T Cell Metabolism in Infection. Front. Immunol. 13:840610. doi: 10.3389/fimmu.2022.840610

T LYMPHOCYTES AND THEIR SUBSETS ARE PIVOTAL CELLS OF THE IMMUNE SYSTEM

All multicellular organisms are in an "arms race" against infectious pathogens, which include pathogenic bacteria, viruses, fungi and parasites (1). The primary defenses against infectious pathogens are the physical and chemical barriers of the skin and mucosa, which separates the external and internal environments (1). Breach of these barriers allow pathogens to enter the body, requiring activation of the immune system to clear the infection (2). The immune system is a host defense system comprising many biological structures and processes within an organism that defends against foreign infection as well as damaged and transformed cells. The ability of the immune system to act optimally depends on its capacity to distinguish foreign and self and to react to non-self. In higher organisms, the immune system is classified into the innate and adaptive immune system (3). The innate immune system is rapidly engaged in an unspecific manner to foreign pathogens or damaged self through recognition of pathogen-associated molecular patterns (PAMP) or damage-associated molecular patterns (DAMP) (4, 5). In contrast to the innate immune system, the adaptive immune system is activated over a longer time-period and is associated with controlled activation of T- and B lymphocytes (T- and B cells), with immense specificity towards its targets, and immunological memory (5). B cells are activated and differentiate into plasma cells that produce immunoglobulins (Ig), commonly referred to as antibodies, following interaction between soluble antigens binding to the B cell receptor (BCR). T cells on the other hand are activated through cell-to-cell interactions when the T cell antigen receptor (TCR) complex encounters peptide antigens presented to them by antigen presenting cells (APC). APCs present antigens through major histocompatibility complex I or II (MHCI and MHCII), which interact with the two major subsets of T cells, CD8 positive (CD8+) and CD4 positive (CD4+) T cells, respectively. CD8+ T cells are also called cytotoxic T lymphocytes (CTLs) while CD4+ T cells are designated as T helper cells (Th) (2). The CTLs target virus-infected cells and induce cell death by three mechanisms.

The secretion of proinflammatory cytokines, interaction between the Fas ligand and Fas receptor, and the secretion of cytolytic granules containing perforin, which creates pores in the target cell allowing the entry of proteases, including Granzyme B, that induce apoptosis (6, 7). CD4+ T cells are indirectly involved in clearing infection by modulating the activity of other immune cells, including macrophages (Mø), neutrophils, B cells and CTLs (2). CD4+ T cells can be grouped into several subsets and include T helper (Th) 1 (Th1), Th2, Th9, Th17, Th22 as well as follicular helper T (Tfh) cells and regulatory T cells (Tregs). The CD4+ T cell subsets are defined by the distinct expression of surface molecules and endogenous production of cytokines, which are driven by the presence of extracellular cytokines and activation of key transcription factors (8). Tfh cells are primarily involved in promoting survival, proliferation and class-switching of germinal center B cells and support germinal center development. Th1, Th2, Th9, Th17, and Th22 subsets, on the other hand, are involved in host defense against specific microbial pathogens. The Th1 and Th2 subsets were the first Th cell subsets to be identified. Whereas Th1 cells kill intracellular bacteria through activating Mø and CTLs, Th2 cells are drivers of immune reactions directed against extracellular parasites (8, 9). Th17 cells, which are characterized by the transcription factor retinoic acid receptor (RAR)-related orphan receptor γ (RORγ) and production of the cytokines IL-17A, IL-17F, IL-21 and IL-22, are involved in protection against pathogens on mucosal surfaces (8, 10–12). Th22 cells also secrete IL-22, but in contrast to Th17 cells, do not secrete IL-17 nor express RORγ (13). As Th22 cells are mainly found in the skin where IL-22 induces expression of antimicrobial peptides in keratinocytes and epithelial cells they are likely involved in maintaining homeostasis in skin (13, 14). Th9 cells, which are characterized by the secretion of IL-9, are involved in immune responses towards extracellular parasites, allergic inflammation and anti-tumor immune response. Interestingly, the anti-tumor functions of Th9 cells were found to be superior as compared to Th1 and other Th subsets and involves activation of the innate and adaptive immune system, including, generation of a profound CTL response against neo antigens (15, 16). Recently, it has also become evident that CD4+ subset of T cells can be cytotoxic themselves. These cytotoxic CD4+ T cells can induce cell death through interacting with peptides presented on MHC II, similar to CD8+ CTLs (17). While the CD4+ subsets are crucial in clearing infection, dysregulation may also result in pathological conditions including autoimmune diseases, allergy and asthma (14, 15, 18, 19). While Th1 and Th17 cells are implicated in autoimmunity and Th2 cells are involved in allergic immune responses, Th22 cells appear to be involved in both autoimmunity and allergy (14, 20–22). Th9 cells have recently been implicated in tumor immunity and promoting tolerance to transplanted organs (15, 23, 24). The activities of T cell subsets are balanced in part by unique CD4+ Treg T cell subpopulation. Tregs are vital to immune homeostasis and self-tolerance, dampening inflammation, and preventing the development of autoimmune disease, but may also be involved in promoting cancer progression (25). The balance between pro-inflammatory and anti-inflammatory signals is critically important.

It is widely accepted that the fundamental processes in T cell biology, such as T cell activation, differentiation and effector functions are closely linked to changes in the cellular metabolic programs. Key metabolic pathways such as glycolysis, fatty acid synthesis and mitochondrial metabolism play a crucial role in T cell immunometabolism (26).

T CELL METABOLISM: FROM QUIESCENCE TO EFFECTOR FUNCTION

T cell metabolism is crucial for maintaining homeostasis in naïve and memory cells, while also priming cells for rapid activation. Additionally, T cell metabolism drives and mirrors the activation and differentiation states of T cells. The focus of this section will be on how activation of T cells and metabolism are related as well as how metabolic reprograming drives the phenotype of activated T cells.

Naïve T cells enter the circulation from the thymus and are actively maintained in a reversible form of cell cycle arrest by a combination of self-peptide–MHC engagement of the TCR/CD3 and by interleukin (IL)-7 stimulation (27). Activation of T cells leads to exit of the quiescent state, inducing cell growth, clonal expansion and differentiation. This process is initiated and regulated by three key factors, perturbation of cell surface receptors, nutrient availability and oxygen levels (28).

The magnitude of acute T cell activation depends on activation of the TCR and co-stimulation of a group of T cell surface co-receptors. These co-receptors include the CD3, CD4, CD8 CD28/CTLA4 and more (29). As mentioned, the CD4 and CD8 molecules directly interact with the MHC II and MHC I molecules, respectively, and influence the early mode of T cell activation. Interaction between the MHC-peptide complex and CD4/CD8 co-receptors is recognized by the TCR, leading to activation of a signaling complex composed of the protein tyrosine kinase (PTK) C-terminal Src kinase (Csk) and lymphocyte-specific protein kinase (Lck). These kinases phosphorylate the immunoreceptor tyrosine kinase-based activation motifs (ITAMs) on the ζ-chain of CD3. This induces downstream signaling by the recruitment, phosphorylation and activation of the zeta-chain associated protein kinase 70 (ZAP70). ZAP70 initiates a downstream signaling cascade and includes activation of phospholipase Cγ1 (PLCγ1), which promotes calcium mobilization, activation of protein kinase C (PKC) and activation of Ras pathway (30–32). The combination of these signaling cascades promotes activation of several transcription factors, including Nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB), Nuclear factor of activated T-cells (NFAT) and Activator protein 1 (AP-1). This leads to production and secretion of the T cell-specific growth factor IL-2 (33–38). The costimulatory receptor CD28 interacts with its ligands CD80 and CD86, which are differentially expressed by APCs. CD86 is constitutively expressed on APCs, while expression of CD80 is induced by stimulation of Toll-like receptors (TLRs)

(39). Activation of CD28 leads to cross phosphorylation of intrinsic CD28 receptor tyrosine residues followed by attachment and activation of phosphatidylinositol kinase 3 (PI3K) (40, 41). PI3K phosphorylates phosphatidylinositol 4,5-bisphosphate (PIP2) to phosphatidylinositol 3,4,5 phosphate (PIP3), leading to activation of protein kinase B (PKB or Akt) and NFκB. This pathway regulates T cell survival through the expression of the anti-apoptotic gene B-cell lymphoma-extra-large (BCL-XL) and Akt-dependent upregulation of IL-2 production (39). CTLA4, however, is considered an inhibitory receptor and stimulation will, to some extent, suppress TCR/CD3-CD28 induced activation by competing with CD28 for CD80/86. Perturbation of the CTLA4 receptor will lead to the recruitment of endogenous protein tyrosine and serine/threonine phosphatases. This includes Src homology protein 2 domain-containing tyrosine phosphatase 2 (SHP-2) and protein phosphatase 2A (PP2A). This will lead to dephosphorylation and inhibition of several proteins in the signaling pathway, including ZAP70, consequently reducing the activation, growth and clonal expansion of T cells (42–47). Exhausted T cells (see below for an explanation) may be found in the environment of chronic infections and cancer cells often display increased expression of inhibitory receptors, including CTLA4 and programmed death receptor 1 (PD-1) (45, 48).

Naïve T cells have relatively low metabolic activity (49), but in response to activating stimuli, metabolic activity is rapidly increased (50). This rapid response is possible due to increased nutrient uptake post stimulation. This may occur concomitant with the presence of untranslated mRNA, idle ribosomes, rapid turnover of transcription factors required for T cell activation, and the presence of an abundance of most of the glycolytic enzymes in quiescent T cells. Together this facilitates upregulation of protein, DNA and lipid synthesis (51, 52). Perturbation of the TCR/CD3 complex and the CD28 marker is further associated with activation of Calcium Calmodulin-dependent protein kinase 2 (CaMKK2) (53). CaMKK2 is known to activate the energy sensor AMP-dependent protein kinase (AMPK) in T cells (54, 55). AMPK is an energy sensor, which is mainly activated by low levels of ATP and liver kinase B1 (LKB1)-dependent phosphorylation (56). Although AMPK is commonly activated in response to an increased ADP/ATP ratio, TCR/CD3-CD28 signaling increases mitochondrial biogenesis and activation of this energy associated enzyme independently of the ADP/ATP ratio (55). This suggests that AMPK activation and increased mitochondrial biogenesis is induced in preparation for the energy demands required for T cell growth and proliferation. Engagement of TCR/CD3-CD28 also promotes recruitment of PI3K and activation of Akt in the immune synapse. This regulates the activity of the mammalian target of rapamycin, mTOR/raptor complex 1 (mTOR complex 1/mTORC1) through inhibition of the key upstream regulator tuberous sclerosis complex 2 (TSC2), which functions as a GTPase activity protein (GAP) for Ras homolog enriched in brain (Rheb) GTPase (57). mTOR kinase forms two distinct protein complexes, mTORC1 and mTORC2, which are crucial for driving differentiation of CD8+ and CD4+ T cells (58). The mTORC1 complex is defined as regulatory-associated protein of mTOR (RAPTOR), while mTORC2 is defined as rapamycin insensitive companion of mTOR (RICTOR) (57).

The GTP-bound form of Rheb directly interacts with mTORC1, which tunes the induction and activity of several transcription factors involved in regulation of mitochondrial activity and biomass production. This includes sterol regulatory element-binding proteins (SREBP) hypoxia-inducible factor 1α (HIF-1α) and MYC, resulting in increased glycolysis, glutaminolysis and lipid synthesis (59). mTORC2, on the other hand, is more involved in fatty acid oxidation and negatively regulates CD8+ T cell memory differentiation through Akt-dependent phosphorylation of forkhead box protein O1 (FOXO1) resulting in cytosolic retention (60, 61). mTORC2 directly phosphorylates Akt on Serine 473, thereby, promoting the expression of glucose transporter 1 (GLUT1), activating hexokinase 2 (HK-2) and phosphofructokinase-1 (PFK-1), phosphorylation and expression of 2-phosphofructkinase 6/fructose 2,6-bisphosphatase (PFKFB)-3 and 4. This promotes in increased glucose uptake and glycolysis (summarized in **Figure 1**) (62–65). TCR/CD3-CD28 stimulation is further associated with induction of lactate-dehydrogenase A (LDHA) that converts pyruvate to lactate (66). This metabolic reprograming of T cells result in increased glycolysis and lactate production despite presence of oxygen (67). This process is commonly referred to as the Warburg effect and supports accumulation of glycolytic intermediates that can enter the pentose phosphate pathway (PPP), to produce ribose 5-phosphate (R5P), which is used in nucleotide synthesis. The Warburg effect is also associated with the production of nicotinamide adenine dinucleotide phosphate (NADPH), which has two main functions; it acts as a redox agent and is essential as an electron donor in anabolic biomass synthesis (67, 68). TCR/CD3 and CD4/CD8-induced PTK activity phosphorylates the muscle form of pyruvate kinase (PKM2) leading to nuclear localization of PKM2 dimers, which participate in regulating gene expression rather than glycolysis (69). In fact, regulation of PKM2 activity is a key factor together with pyruvate dehydrogenase kinase 1 (PDK1) in preventing pyruvate entering the mitochondrion. PDK1 inhibits the enzyme pyruvate dehydrogenase (PDH), which catalyzes the formation of acetyl co-enzyme A (AcCoA) and TCA cycle entry. This leads to accumulation of pyruvate in the cytosol, which is used to produce lactate and regenerate NAD+ from NADH (70, 71).

Many proliferating cells, including TCR/CD3-CD28 stimulated T cells, may adopt profiles associated with oxidative phosphorylation (OXPHOS) when glucose is limited. This is achieved by increased uptake and metabolism of the amino acid glutamine (72). This requires upregulation of the glutamine transporter, alanine-serine-cysteine transporter 2 (ASCT2/SLC1A5) and differential regulation of the glutaminase (GLS) isoforms, kidney glutaminase (KGA) and glutaminase C (GAC) (73, 74). TCR/CD3-CD28 co-stimulation upregulates expression of GAC, while downregulating KGA. GLS catalyzes the deamidation of glutamine to glutamate, which is the first step of glutaminolysis. Glutaminolysis is mainly regulated through MYC-induced expression of key genes (75). Glutamine

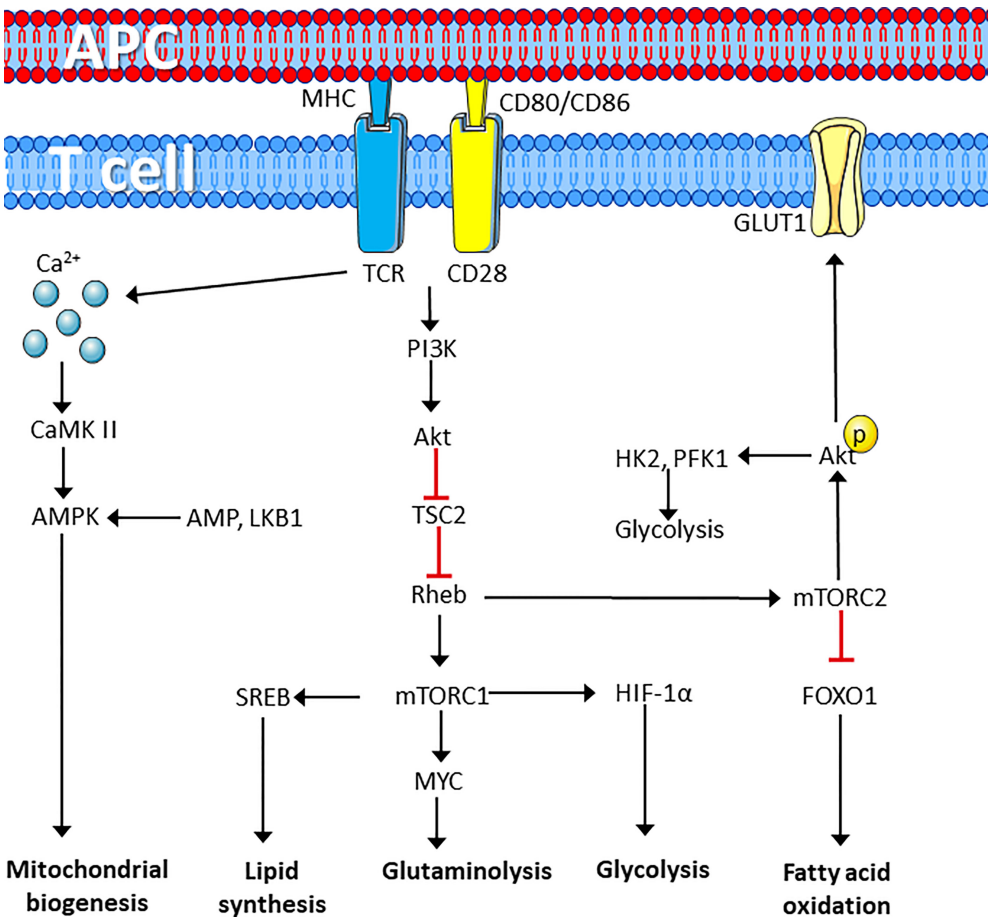

FIGURE 1 | T cell receptor perturbation drives metabolic reprograming. T cell activation by ligation of the TCR and CD28 cell surface marker induces metabolic reprograming through activation of protein kinases that induces calcium dependent activation of the AMPK pathway to induce synthesis of mitochondria. In addition, mTORC1 activation induces lipid synthesis and enhances lipid synthesis, glutaminolysis and glycolysis required for rapid proliferation, whereas mTORC2 induces glucose uptake and glycolysis while repressing fatty acid oxidation. Figure was created using assets from Servier Medical Art, licensed under a Creative Common Attribution 3.0 Generic License. (http://smart.servier.com/). APC, antigen presenting cell; TCR, T cell receptor; PI3K, phosphatidylinositol kinase 3; CaMK II, calcium calmodulin-dependent kinase II; AMPK, adenosine monophosphate-dependent kinase; TSC2, tuberous sclerosis complex 2; Rheb, RAS homolog enriched in the brain; LKB1, liver kinase B1; SREB, sterol regulatory element-binding proteins; HIF-1α, hypoxia-inducible factor 1 α; mTORC, Mechanistic target of rapamycin complex; GLUT1, Glucose transporter 1; FOXO1, forkhead box O1; FAO, fatty acid oxidation; HK1, hexokinase 1; PFK-1, phosphofructokinase 1.

metabolism is crucial for proliferating cells as it is involved in several metabolic pathways. This includes production of α-ketoglutarate (α-KG) from glutamate and alanine by transferring the amino group from glutamate to pyruvate by alanine aminotransferase (ALT) (76). The product, α-KG may enter the TCA cycle to form citrate. Citrate can be shunted out of the mitochondrion to support cytosolic AcCoA levels and used as a substrate lipogenesis and mevalonate metabolism as well as cholesterol synthesis (77, 78). α-KG may also support production of carbon intermediates in the TCA cycle and the production of reduced forms of the electron donors NADH and flavin adenosine dinucleotide (FADH) required for OXPHOS (79). Glutaminolysis also supports production of NADPH through the PPP and TCA cycle, which along with glutamate and cysteine, is used to produce the antioxidant glutathione (GSH) (80, 81). Finally, glutaminolysis provides both carbon and nitrogen residues used for synthesis of polyamines, amino acids and DNA and RNA nucleotides (82). Inhibition of glutaminolysis as well as reduced ornithine and putrescine synthesis decrease T cell proliferation, highlighting the important role of glutaminolysis (83).

As glutamine has a central role in proliferating cells, including activated T cells, glutamine is sometimes referred to as a conditionally essential amino acid. In fact, exogenous glutamine deprivation and inhibition of glutaminolysis prevent T cell activation, proliferation and clonal expansion (84). This reliance on glutamine metabolism is sometimes referred to as "glutamine-addition". Glutamine-dependent anapleurosis is further known to dictate glucose uptake and glycolysis in proliferating cancer cells (85, 86). Extracellular glutamine depletion is also associated with metabolic reprogramming, as glutamine synthetase (GS) converts glutamate to glutamine, is

upregulated (87). Glutamine anapleurosis can also be used to produce the amino acid asparagine, which in addition to being important for protein synthesis, is also regulating activation of T cells by directly enhancing Lck activity (88–90). In response to glutamine deprivation, asparagine becomes an essential amino acid. Despite this, mammals do not possess functional asparaginase, the enzyme required for asparagine to re-enter the TCA cycle (89). In fact, ectopic expression of the catalytically active asparaginase inhibits cell growth and proliferation by redirecting asparagine to the TCA cycle rather than protein synthesis (89, 91). Arginine is another amino acid important for T cell activation, and supplementation of extracellular arginine increases long-term survival and effector functions of T cells, accompanied by a reduction in glycolysis and enhanced oxidative phosphorylation (92). T cell activation and clonal expansion also require uptake of the amino acids cysteine, methionine and the branched chain amino acid (BCAA) leucine. While naïve T cells do not express transporters for cysteine and cystine, this is rapidly induced by CD3/CD28-induced activation. In early activation, uptake of cysteine and methionine is crucial for proliferating T cells (93). Leucine is important for determining the fate of CD4+ T cells as it regulates activation of mTORC1. During leucine depletion the leucine sensor sestrin 2 (SESN2) binds to the GTPase-activating protein towards Rags-2 (GATOR2), forming an inhibitory complex towards mTORC1 (94, 95). Loss of the leucine transporter SLC7A5/LAT1 (CD98) limits T cell activation and effector maturation owing to impairments in mTORC1 activity (96). Finally, serine is used for one-carbon metabolism and purine synthesis through the B vitamin 10-formyltetrahydrofolate. Serine also supports 5-methyltetrahydrofolate, and generation of the methyl donor S-adenosyl methionine (97).

In addition to nutrient availability, oxygen tension also varies greatly in different tissues. Many lymphoid organs, including spleen and thymus, are known to have low oxygen levels and are considered to be in a state of physiological hypoxia (<4% O_2) (98). T cells, which are highly mobile in nature encounters a wide range of oxygen levels in the body. For example, during thymic development, thymocytes inhabit within relatively low oxygen (< 1%). Activated T cells are faced with both high oxygen levels in the lungs and arterial blood as well as the hypoxic and anoxic conditions in inflammatory lesions and tumors (99–101). As low oxygen concentration is metabolically challenging, hypoxia induces metabolic programs required to adapt to the environment. T cell differentiation, function and survival is known to be affected by exposure to hypoxia, a response mainly mediated by the transcription factor HIF-1α, directly or indirectly (98). HIF-1α, is stabilized and heterodimerizes with the constitutively expressed HIF-1β, also known as aryl hydrocarbon receptor nuclear transporter (Arnt) under hypoxic conditions. The HIF complex translocate into the nucleus where it binds to hypoxia response elements (HREs) (102). In the presence of oxygen, HIF-1α is rapidly degraded by the enzyme prolyl hydroxylase domain proteins (PHD) 1, 2 and 3, thus the HIF-1α complex has limited transcriptional activation capacity in normoxia. HIF-1α induces a metabolic shift by inducing a glycolytic phenotype mediated by increased expression of genes involved in glucose uptake and glycolysis, including GLUT1, HK2, PKM2, LDHA, while actively reducing glucose oxidation through the expression of PDK1 (102–104). This indicates that HIF-1α induces a metabolic phenotype where glycolysis is the primary source for ATP. As pyruvate is shunted towards lactate, rather than the TCA cycle, this reduces the ability to produce citrate. To compensate for this, cells at hypoxia produce citrate and cytosolic AcCoA required for fatty acid synthesis through glutaminolysis. In this case, α-KG is metabolized to citrate through the TCA cycle in a reverse fashion by reductive carboxylation. These reactions are catabolized by the two isocitrate dehydrogenase (IDH) isozymes, IDH1 and IDH2, which are induced by low oxygen (105, 106). This demonstrates that during hypoxia, HIF-1α drives T cells to adapt a metabolic phenotype relying on glycolysis and glutaminolysis to support proliferation and clonal expansion.

In addition to its role in early activation, it has become increasingly clear that distinct metabolic programs define the various T cell subsets (**Figure 2**) (107). It is also known that T cell differentiation can be manipulated through modulating metabolic activity *in vitro* (108–110). However, the extent of how metabolism affects T cell function in response to infection is not fully understood.

As mentioned, naïve T cells generate most of their ATP from oxidative phosphorylation and in general display a less energetic state than activated T cells yet can rapidly reprogram metabolism upon activation (50, 111, 112). This rapid response towards antigen is likely made possible by the rapid turnover of proteins (51). While this metabolic reprograming stems, at least in part, from an increased demand for ATP to fuel rapid proliferation, there is also increasing evidence that fine-tuning of specific metabolic pathways drive differentiation into various subsets. This is best characterized for the Th1, Th2 and Th17 subsets.

Th1, Th2 and Th17 cell differentiation induces three distinct metabolic phenotypes. However, all subsets have a relatively high rate of glycolysis when compared to Tregs, naïve or memory T cells (113). While Glucose is known to be crucial for T cells to produce IFNγ, as cells cultured in galactose have severely reduced IFNγ-secretion. This has been linked to the dual role of the enzyme glyceraldehyde 3-phosphate dehydrogenase (GAPDH), as it can bind to, and repress translation of IFNγ mRNA (110). This was shown to be related to glucose-derived mannose combustion. Supplementation with mannose could partially restore IFNγ production in cells cultured with the glycolysis inhibitor 2-deoxy-D-glucose (2DG). Interestingly, the transcription factor T-bet, which is crucial for Th1 differentiation, was reduced when cells were cultured in the presence of galactose, but was restored by mannose supplementation (114). Lastly, inhibition of GLS-1 has been shown to increase Th1 differentiation (73). Th2 cells are reportedly the most glycolytic of the Th subsets, correlating with high expression of GLUT1 and low rate of fatty acid oxidation (113). mTORC2, which as previously mentioned, is an important regulator of fatty acid oxidation and glycolysis, is also important for differentiation of Th1 and Th2 cells through distinct mechanisms. Th1 cells depend on mTORC2-dependent phosphorylation of Akt, while Th2 cells depend on phosphorylation

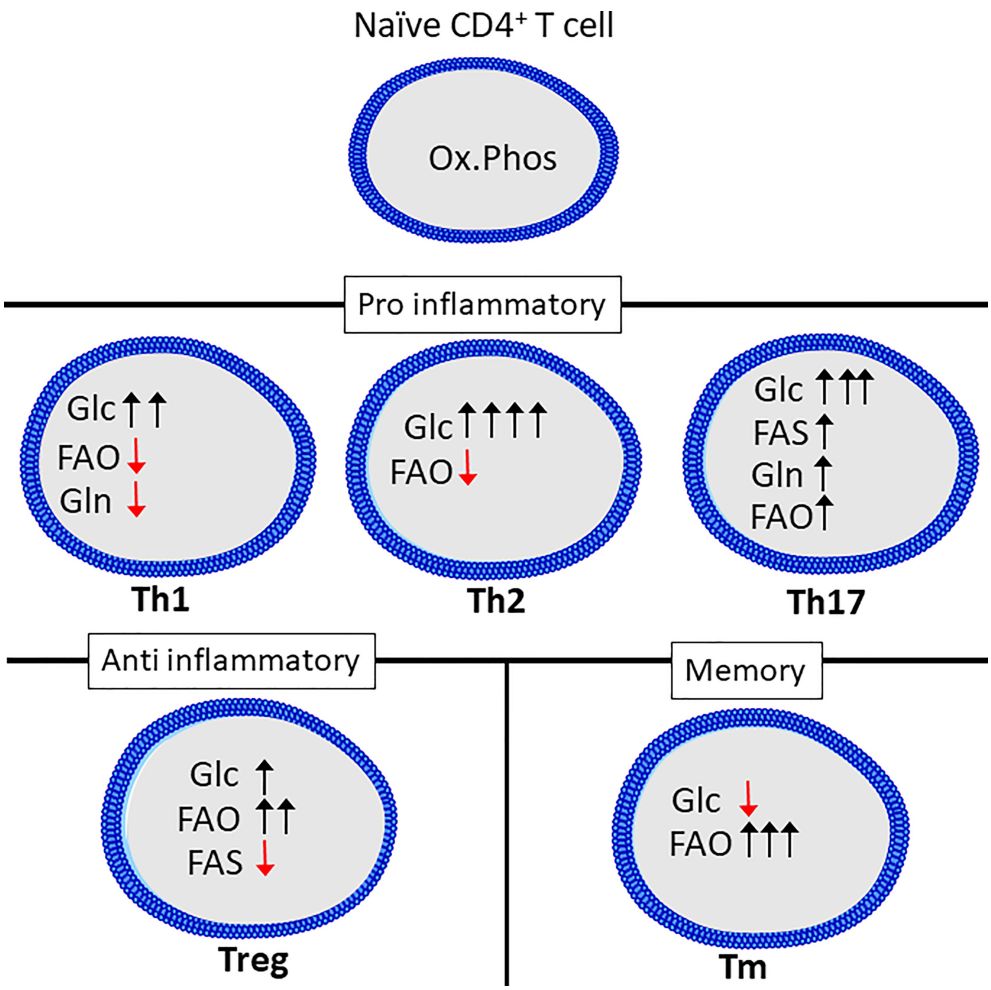

FIGURE 2 | Th subsets display distinct metabolic programs. Quiescent Th cells rely mainly on oxidative phosphorylation (Ox.Phos) to maintain homeostasis, while the effector subsets are characterized by increased glycolytic metabolism (Glc) as well as a differential reliance on glutaminolysis (Gln), fatty acid oxidation (FAO and fatty acid synthesis (FAS) to support effector functions. Figure was created using assets from Servier Medical Art, licensed under a Creative Common Attribution 3.0 Generic License. (http://smart.servier.com/t).

of PKC (115). Peroxisome proliferation activating receptor-γ (PPAR-γ), which is a regulator of fatty acid metabolism, is also involved in promoting Th2 differentiation while repressing Th1 differentiation (116). Th17 differentiation induces a metabolic phenotype distinct from both Th1 and Th2 cells. Th17 differentiation requires HIF-1α stabilization and induction of PDHK1, preventing mitochondrial pyruvate oxidation in favor of lactate production (71, 104, 117). GLS1-dependent glutamine metabolism is also a crucial factor for Th17 differentiation (109). GLS1 expression in T cells can be induced by the transcription factor inducible cAMP early repressor (ICER) (109). Blocking GLS1 shifts Th17 cells to a Th1-like phenotype (73). Th17 differentiation also requires fatty acid synthesis (118). The metabolic phenotype of Th9 and Th22 cells is not as extensively studied compared to that of the other CD4+ effector cells. However, Th9 cells have a higher glycolytic rate than both Th2 and Th17 cells, and require activation of mTORC1 and HIF-1α (119).

Treg differentiation depends on the oxidation of long fatty acids, induced by activation of AMPK (113). Although Tregs upregulate glycolysis compared to naïve cells this is to a lesser degree than the effector CD4+ T cells and it is not necessary to support Treg differentiation (113, 120). In support of this Treg differentiation is inhibited in favor of Th17 differentiation by HIF-1α-induced glycolysis (117, 121). In fact, increasing glucose uptake and glycolysis in Tregs represses suppressor functions despite increasing proliferation (122, 123). Compared to effector CD4+ T cells, Tregs depend on fatty acid oxidation to fuel mitochondrial respiration (120). Treg differentiation may also be reduced by the presence of exogenous amino acids including glutamine, tryptophan and arginine (124). Lastly, extracellular lactate may enhance Treg function through uptake *via* the monocarboxylate transporter 1 (MCT1) (123).

Memory subsets of T cells are characterized by a reliance on fatty acid oxidation and low rate of glycolysis (125).

Supplementing the amino acid arginine has been shown to enhance memory formation and reprogram T cells from a glycolytic to an oxidative phenotype (92). Similar to naïve T cells, memory T cells have a rapid turnover of proteins related to activation, including glycolytic enzymes (51).

The microenvironment is also important for modulating T cell activity and metabolism. Recently, it was discovered that T cells create acidic niches within lymphoid organs to dampen effector functions (126). This is also well-defined in the tumor microenvironment (TME), which is characterized by the presence of anti-inflammatory cytokines, low levels of oxygen and acidification by lactate (127–130). In rheumatoid arthritis the microenvironment of the synovium exerts pro-inflammatory effects on the CD4+ T cells by repressing glycolytic rate (131). It is further known that increased body temperature may enhance proliferation and effector functions of both CD4+ and CD8+ T cells (132, 133) Together this demonstrates how the microenvironment may shape T cell activity.

T cell exhaustion is featured in both cancer and persistent infections. Exhausted T cells can be defined by an increased expression of inhibitory ligands, including PD-1 and CTLA-4 and are more apoptotic than effector and memory cells (48, 134). Exhausted T cells also display a distinct metabolic phenotype, with reduced glucose uptake as well as mitochondrial dysfunction, which reduces capacity for oxidative metabolism. The presence of extracellular metabolites as well as low abundance of important nutrients may further inhibit metabolism and prevent the appropriate T cell activity (135, 136).

T CELL METABOLISM IN INFECTION

As detailed above, T cell metabolism and functionality are closely related and metabolic reprograming is crucial for appropriate T cell activity. In this section, we will briefly describe how T cell metabolism is regulated in certain acute infections and how T cell metabolism may aid or hinder pathogen clearance under acute and chronic conditions of infection. We will use examples of virus infections by SARS-CoV-2 and HIV as these viruses are known to induce differential effects on T cell metabolism. We will also briefly describe T cell metabolism in bacterial infections, here exemplified by infections of Mycobacterium tuberculosis.

T Cell Metabolism in SARS-CoV-2 Infections

When T cells are engaged in the immune response, they can be roughly divided into naïve, effector and memory cells, each with accompanying metabolic programs (137). The immune system, when properly regulated will have a protective role. However, in some cases the immune system might exasperate the inflammation associated with infection (138). This is apparent for SARS-CoV-2 infections, which cause the well-known coronavirus disease 2019 (COVID-19). Despite that the underlying molecular mechanism responsible for sustaining SARS-CoV-2 virulence is enigmatic, how SARS-CoV-2 attaches on the surface of host cells through a variety of receptors is in part well described. Attachment may be through receptors, such as angiotensin converting enzyme 2 (ACE2), neuropilin-1 (NRP1), AXL, and antibody–FcγR complexes (139). ACE2 is expressed in various human organs and may play a role in regulating cardiovascular and renal function. In addition, the ACE2 protein is a functional receptor for the spike glycoprotein of the human coronavirus and is considered a causative agent of COVID-19 disease. Next, NRP1 is a membrane-bound coreceptor to a tyrosine kinase for both vascular endothelial growth factor (VEGF) and semaphorin (SEMA3A) family members, both playing versatile roles in angiogenesis, axon guidance, cell survival, migration, and invasion. Furthermore, the gene AXL, which encodes the tyrosine-protein kinase receptor UFO, is involved in stimulation of cell proliferation and survival through PI3K-AKT-mTOR, MEK/ERK, NF-κB, and JAK/STAT activation (140–143). In line with the fact that COVID-19 uses receptor ligation for infection, several reports reveal that COVID-19 ligation through and activation of the above-mentioned signal transduction molecules, induces metabolic reprogramming (144, 145). In fact, this metabolic reprograming can be detected by positron emission tomography (PET) by increased accumulation of ^{18}F labelled fluorodeoxyglucose (FDG) (146). This metabolic reprograming is also associated with a distinct profile of serum metabolites, which might be used as a prognostic measurement of disease severity (147). It has further been demonstrated that this increased level of FDG in the tissue correlate with increased glycolysis in several cells, including epithelial cells and immune cells, reviewed by Kumar (148). Notably, peripheral blood mononuclear cells (PBMCs) display metabolic dysfunction, characterized by increased glycolysis and reduced oxygen consumption (149). SARS-CoV 2-infected monocytes also show enhanced glycolytic rate. Interestingly, the same study reports that increasing extracellular glucose concentration increased SARS-CoV 2 replication in monocytes (150). Because of this central role of glycolysis in COVID-19 the glucose analog 2-deoxy-D-glucose (2DG), which inhibits glycolysis, has undergone a phase III trial and received emergency approval in the treatment of moderate and severe COVID-19 in India. However, the trial was conducted in only 220 patients and the data has not been made available to the public (151). In this review we have mainly focused on the metabolism of T cells in response in COVID-19.

In both CD4+ and CD8+ T cells COVID-19 inhibits activation of mTORC1, which reduces glycolytic activity, as well as causing mitochondrial dysfunction and increased susceptibility to apoptosis (**Figure 3**) (145). In line with this, expression levels of GLUT1 are reported to be decreased in T cells in patients with severe COVID-19 as compared to healthy controls or patients infected by influenza virus. However, contradictory results exist. A study by De Biasi et al., showed with one exception that T cells from COVID-19 patients had a similar capacity for metabolic reprogramming to non-infected T cells (152). However, the COVID-19 patients all required respiratory aid, while most patients in the latter study had pO_2 >90%. This might indicate a link between metabolic alteration, mitochondrial dysfunction and declining oxygen saturation (145, 152). This is supported by a study by Siaska et al., where T cell metabolism was differentially affected in mild compared to

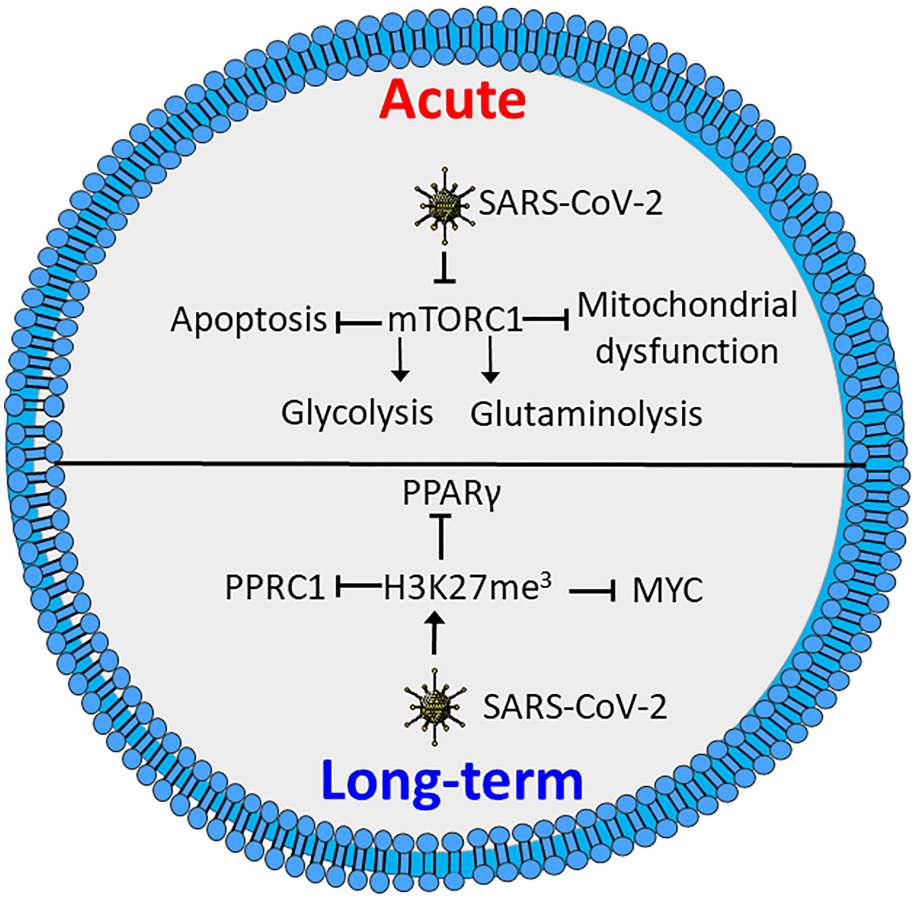

FIGURE 3 | SARS-CoV-2 induces metabolic defects in acute and long-term infection. Acute infection by SARS-CoV-2 inhibits activation of mTORC1, causing reduced glycolysis and glutaminolysis as well as enhanced apoptosis and mitochondrial defects. Long-term SARS-CoV-2 induces triple methylation of histone 3 lysine 27 ($H3K27me^3$), resulting in reduced activation through inhibition of MYC peroxisome proliferator-activated receptor γ (PPARγ) and peroxisome proliferator-activated receptor gamma coactivator-related protein 1 (PPRC1). Figure was created using assets from Servier Medical Art, licensed under a Creative Common Attribution 3.0 Generic License. (http://smart.servier.com/).

moderate and severe disease. This was evident by an elevated uptake of fatty acids in T cells from patients with mild or no symptoms, while glucose uptake was similar to that of quiescent T cells from healthy controls (153). This study also revealed that moderate and severe disease was correlated with increased mitochondrial content, ROS and expression of basigin, which is reported to drive hyperinflammation and bone degradation in rheumatoid arthritis (153, 154).

Several studies have shown that recovered COVID-19 patients display symptoms for weeks or months after disease onset, commonly referred to as "long COVID" (155–157). These symptoms include chest pains, joint pains, cognitive disorders, anxiety, depression and neurological disorders. Long COVID even affects individuals who initially had mild symptoms upon infection (155, 156, 158). Interestingly, T cells from COVID-19 patients reportedly have increased levels of triple methylated histone 3 lysine 27 ($H3K27me^3$), a potentially epigenetic effect that persists in recovered patients (159). Reports demonstrate that the $H3K27me^3$ modification represses T cell activation, differentiation and metabolic activity, by inhibiting expression of several transcription factors involved in metabolic regulation. These include MYC, PPARγ and peroxisome proliferator-activated receptor gamma coactivator-related protein 1 (PPRC1) (**Figure 3**) (160, 161). A recent study demonstrates a correlation between neurologic symptoms in recovered patients and T-cell immune reactivity. Patients with neurologic symptoms were also shown to have a distinct T-cell phenotype compared to healthy COVID convalescents. Notably, in individuals with long COVID Tfh cells had increased reactivity to the nucleocapsid of the SARS-CoV-2 virus, while the COVID convalescents showed reactivity towards spike proteins (157). This is consistent with an earlier study revealing that T cells from patients with neurological symptoms following COVID-19 recovery, displayed a distinct reactivity. The same study also showed an increase in the population of exhausted CD4+ T cells (162). Whether these effects are related to the epigenetic changes induced by methylation of H3K27 is not clear. Further studies will be needed to determine how T-cell metabolism and

metabolic dysfunction are correlated to COVID-19 disease severity and if similar phenomena can be found for other infectious agents.

As T-cell metabolism is correlated to both short-term survival and long-term effects further studies of T-cell metabolism in COVID-19 may result in better stratification of patients as well as offering new therapeutic targets to minimize the impact of COVID-19.

T Cell Metabolism and HIV Infections

The excessive immune response for severely affected patients may be caused by so called cytokine storms, which is simply defined as release of too many cytokines into the blood too quickly (163). In patients where this occurs, coupled with inability to clear infection leads to chronic infection, a condition leading to T-cell exhaustion (137). Exhausted T cells are characterized by an increased expression of inhibitory markers and a progressive and hierarchical loss of function as seen in HIV infections, where HIV is the causative agent for acquired immunodeficiency syndrome (AIDS) (164). HIV target the CD4 cell surface marker, allowing infection of CD4+ T cells and Mø (165). During the acute phase of HIV infection, most patients experience a marked increase in HIV viral load coupled with increased levels of the PD-1 receptor on HIV-infected T cells. Untreated patients will in this case experience T-cell exhaustion. The positive effects of antiretroviral therapy (ART), which in most cases significantly inhibits viral replication, also lowers high PD-1 expressing T cells, suggesting a link between viral load and the level of PD-1 expressing T cells (166, 167). The HIV virus infects cells by first interacting with CD4, followed by interaction with the chemokine receptor CCR5 on Mø or CXCR4 on T cells (168). In addition to CD4 and CXCR4, HIV is reported to exploit GLUT1 to infect T cells (169). GLUT1 expression has been shown to be elevated on circulating CD4+ T cells in patients with chronic HIV-1 infection. As HIV-induced surface expression of GLUT1 coincide with increased glucose uptake and increased glycolytic activity (**Figure 4**) (170, 171) it is likely that such a metabolic pattern mirror HIV infected CD4+ T cells in AIDS patients. Recently, it was demonstrated that in acute HIV-1 infections, viral replication is correlated with increased

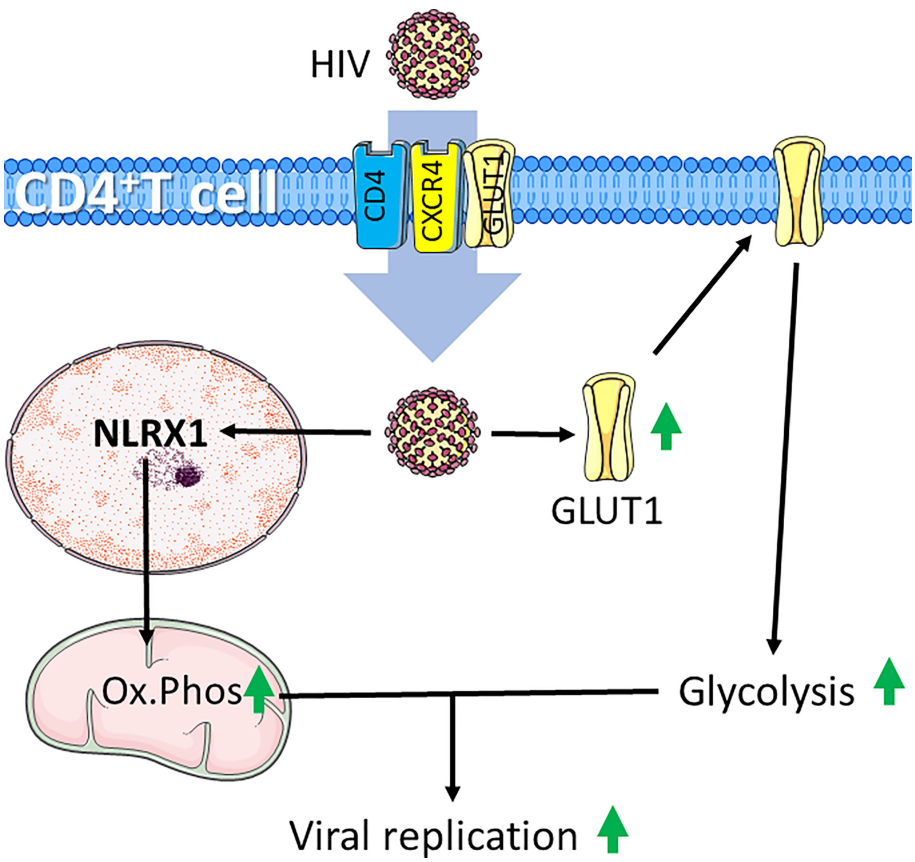

FIGURE 4 | HIV infection induces increased glycolysis and mitochondrial respiration in CD4+ T cells. HIV infects CD4+ T cells through interaction with CD4 and chemokine receptor CXCR4. HIV-infection supports glycolytic metabolism by increasing expression of the glucose transporter GLUT1, which can also be exploited to further infect CD4+ T cells. Additionally, HIV induces expression the of nucleotide-binding domain leucine-rich repeat-containing receptor X1 (NLRX1) to induce increased oxidative phosphorylation (Ox.Phos). The increased metabolic rate supports enhanced viral replication. Figure was created using assets from Servier Medical Art, licensed under a Creative Common Attribution 3.0 Generic License. http://smart.servier.com/.

expression of nucleotide-binding domain leucine-rich repeat-containing receptor X1 (NLRX1). NLRX1 is most likely required for the HIV-induced metabolic reprograming of CD4+ T cells and leads to increased glycolysis and oxygen consumption. Interestingly, blocking glycolysis using the glucose analogue 2DG or mitochondrial respiration using rotenone or metformin inhibits HIV replication in CD4+ cells (171). This is in line with the fact that CD4+ T cells cultured with the simple sugar galactose exhibit less viral replication and reduced HIV-induced cell death, supporting that HIV infections requires glycolytic activity (172). Furthermore, some HIV-infected patients maintain low virus titers even without ART. This was associated with distinct HIV-specific CD8+ T cells. Such CD8+ T cells can be distinguished from CD8+ T cells from patients sensitive to ART. In the ART-insensitive patients, the CD8+ T cells expressed enhanced levels of mTORC2 and increased fatty acid oxidation. and ART-insensitive patients were further associated with formation of increased numbers of CD8+ memory T cells Interestingly, in ART treated CD8+ T cells, treatment with IL15 reflected increased mTORC2 expression and a fatty acid consuming phenotype (173). In line with these observations, T-cell metabolism may have prognostic potential, and may even provide therapeutic targets in cases of HIV infections.

The current knowledge of T-cell metabolism in HIV infection indicates that the HIV virus exploits the glycolysis of CD4+ T cells to both infect and enhance replication rate, while high glycolytic rate of CD8+ T cells confer resistance to infection (170, 171, 173). Hence, both CD4+ and CD8+ T-cell metabolic profiles may serve as prognostic markers of the patients. In line with this, it is speculated that targeting glycolysis of e.g., CD4+ T cells may reduce T-cell replication in patients suffering from viral infection, such as by HIV. Importantly, this understanding of metabolism in HIV indicates a potential for repurposing metformin for the management of HIV infection (171). Together, this highlights the importance of further studies to determine the efficacy of metabolic inhibition in the management of HIV infection.

T-Cell Metabolism in Tuberculosis Infections

Tuberculosis remains a major threat to human global health, with an estimated one-fourth of the world population latently infected (174). Tuberculosis is caused by *Mycobacterium tuberculosis* (MT) infection. T cells and Mø are crucial players in the anti-mycobacterial host defense and in containing the spread of mycobacteria during latent disease (175). This is highlighted by the observation that HIV-induced depletion of CD4+ T cells and the level of PD-1 expression leads to increased co-morbidity in MT-infected individuals (176, 177). Together this points to the importance of stringent regulation of CD4+ T cells in defense against MT infection.

With an increasing body of evidence, it is argued that metabolic changes at the cellular level, is vital to mount an effective immune response to MT. This include pathways found to be necessary for the full activation of lymphocytes and include regulation of cytokine production, pyrimidine metabolism, as well as production of glutathione and large amounts of mitochondrial reactive oxygen species (ROS) in response to MT infection (178). To this end, the mitochondrial matrix protein Cyclophilin D (CypD) acts as a peptidyl-prolyl cis-trans isomerase that regulates the mitochondrial permeability transition pore (PTP). PTP is a nonspecific large conductance pore when open leads to cell death. PTP expression has been implicated in ischemia/reperfusion injury in multiple organs, in neurodegenerative disorders, and in muscular dystrophies (179, 180). Interestingly, loss of CypD is implicated in metabolic changes, which include increased aerobic glycolysis, mitochondrial OXPHOS, and consumption of glucose and glutamine. This is further associated with increased T-cell activation to proliferation and cytokine production, such as TNFα and IFNγ. Moreover, MT infection in CypD ablated individuals, lead to immunopathology caused by T-cell dysfunction, however, without affecting bacterial burden. Moreover, CypD-deficient mice succumbed earlier to infection than wild-type mice stressing the role of CypD and dysregulated T-cell function potentially associated with altered immune cell metabolism in MT infections (181). It is also reported that both early and long-term MT infection induces distinct defects to the metabolism of CD8+ T cells. MT infection increases expression of both PD-1 and CTLA4, which further correlates with decreased glucose uptake as well as reduced glycolysis and mitochondrial respiration. This further reflects a repressed metabolic programing normally induced by stimulation of the anti-CD3/CD28 complex (182).

As the tissue microenvironment also affects the effector functions and metabolism of T cells, targeting metabolic pathways can also affect T-cell activity indirectly. This is the case for MT-induced granulomas, in which Mø catabolize tryptophan and secrete transforming growth factor β (TGF-β) to create an immunosuppressive environment (178, 183, 184). Hence, the capability of T cells in clearing MT infections is largely limited by the inability to enter the granulomas in which MT induces expression of indoleamine 2,3-dioxygenase (IDO), and tryptophan catabolism to form the immunosuppressive metabolite kynurenine (185, 186). Moreover, IDO expression has previously been linked to a decline in IFNγ, demonstrating how MT-induced changes in Mø metabolism may induce tolerance and prevent clearance (183). This likely occurs through interaction between kynurenine and the aryl hydrocarbon receptor (AHR) in combination with TGF-β, which drives Treg differentiation (**Figure 5**) (187). In conclusion, MT infections contribute to decreased T cell glycolytic metabolism through several mechanisms. Despite that the knowledge is sparse, such changes may further have implications for how and to what extent the immune system is able to counteract a MT infection and to what extent the immune system may be capable to eradicate the MT bacteria.

CONCLUSION

We have briefly summarized some knowledge on T-cell metabolism in situation of infections by virus and bacteria. Research over the last couple of decades have revealed that T-cell metabolism is closely linked, not only to proliferation and

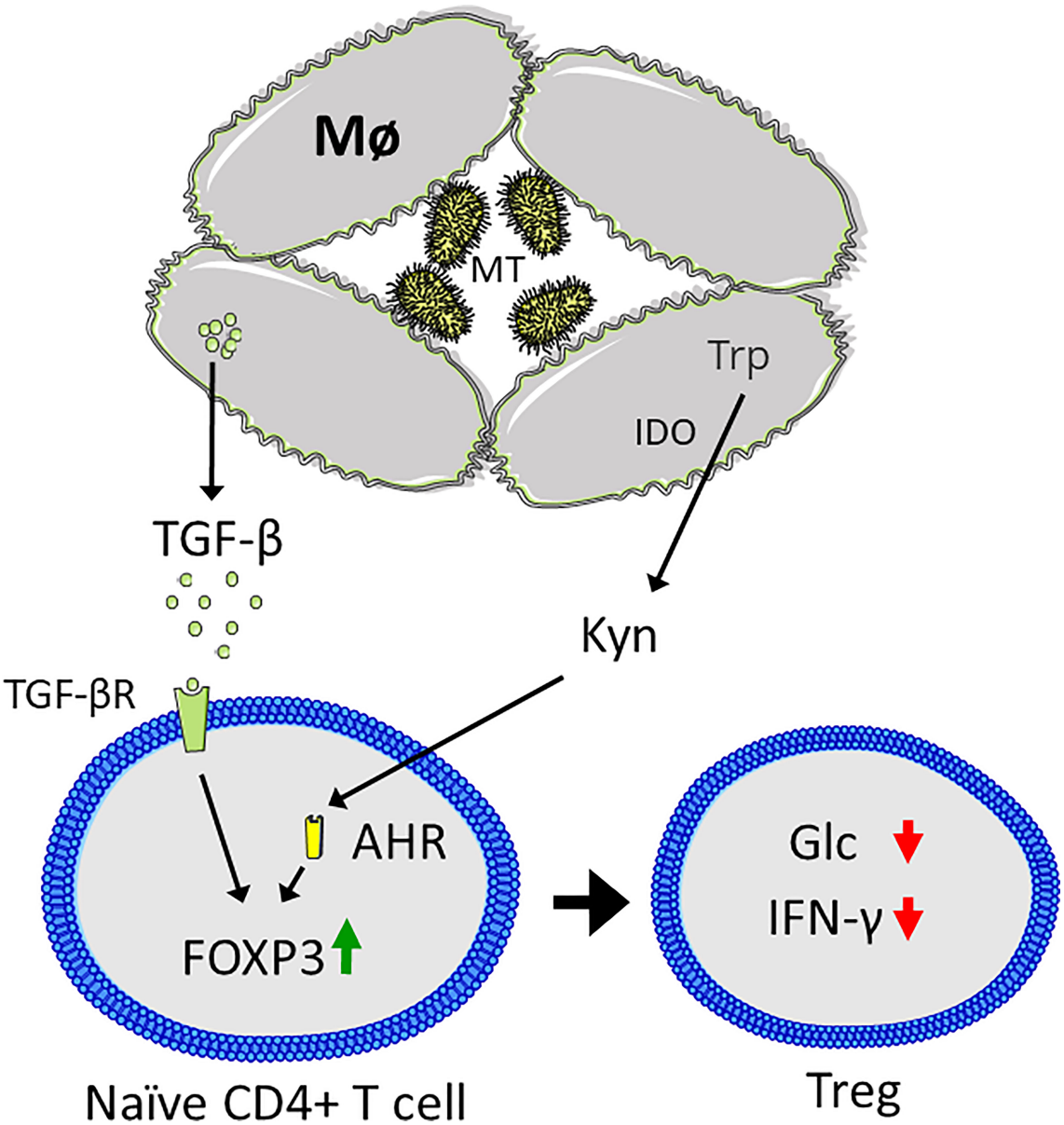

FIGURE 5 | *Mycobacterium tuberculosis* (MT) infection results in an immunosuppressive microenvironment. Macrophages (Mø) are unable to clear MT infection, resulting in granuloma formation. MT induces expression of indoleamine 2,3-dioxygenase (IDO), which catabolized tryptophan (Trp) to kynurenine (Kyn), which binds to the aryl hydrocarbon receptor (AHR) in CD4+ T cells, coupled with secretion of transforming growth factor β (TGF-β) that binds to the TGF-β receptor (TGF-βR). Together this results in upregulation of FOXP3 and Treg differentiation, characterized by suppression of CD4+ T cell glycolysis (Glc) and interferon γ (IFN-γ) secretion. Figure was created using assets from Servier Medical Art, licensed under a Creative Common Attribution 3.0 Generic License. (http://smart.servier.com/).

clonal expansion, but that cell-specific metabolism also dictate cell differentiation programs and reflect effector functions (136). As detailed here, T-cell metabolism may in addition aid pathogen clearance or confer resistance to infections by virus and bacteria. However, in some cases T-cell metabolism may be displayed as T-cell exhaustion leading to tolerance, or even support of inflammation. The latter is displayed in certain cases of viral infection, where immune cell metabolism also supports viral replication (135, 169, 170, 181, 182).

Modulating T-cell metabolism by supplementation with key nutrients or employing inhibitors of key metabolic pathways has previously been shown to enhance memory formation or enhance effector function of T cells in cancer, or even induce pro-inflammatory and migratory programs (92, 108, 188, 189). As T-cell exhaustion is a feature in both persistent infection and cancer it is expected that reversing the exhausted phenotype will have markedly clinical potential (190). T-cell metabolism may also be important in both the acute and long-term effects of

COVID-19, making it an interesting target for therapeutic applications (145, 155, 159, 162).

As detailed in this review, metabolic reprograming of T cells is crucial for conveying protection against infectious pathogens. On the other hand, some pathogens may exploit or modify T cell metabolism to prevent the appropriate effector functions. Further research is needed to determine if targeting dysfunctional T cell metabolism may be used therapeutically in infectious diseases to enhance effector functions and reverse T-cell exhaustion in chronic infections.

AUTHOR CONTRIBUTIONS

JW and BS both conceived and drafted this review and contributed to final proof and approval of the submitted version.

FUNDING

Grant from Thorn Holst 2020-2021 to BS.

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