Biologics: Targets and Therapy

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Targeting Metabolic Reprogramming of T-Cells for Enhanced Anti-Tumor Response

Yosef Tsegaye Dabi[1,2], Henok Andualem[3], Sisay Teka Degechisa[1,4], Solomon Tebeje Gizaw[1]

[1]Department of Medical Biochemistry, School of Medicine, College of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia; [2]Department of Medical Laboratory Science, Wollega University, Nekemte, Ethiopia; [3]Immunology and Molecular Biology, Department of Medical Laboratory Science, College of Health Science, Debre Tabor University, Debre Tabor, Ethiopia; [4]Department of Medical Laboratory Sciences, College of Medicine and Health Sciences, Arba Minch University, Arba Minch, Ethiopia

Correspondence: Yosef Tsegaye Dabi, Tel +251911364465, Email yoseftsegaye01@gmail.com

Abstract: Cancer immunotherapy is an effective treatment option against cancer. One of the approaches of cancer immunotherapy is the modification of T cell-based anti-tumor immune responses. T-cells, a type of adaptive immune response cells responsible for cell-mediated immunity, have long been recognized as key regulators of immune-mediated anti-tumor immunity. T-cell activities have been reported to be suppressed or enhanced by changes in cell metabolism. Moreover, metabolic reprogramming during activation of T cells is required for the development of distinct differentiation profiles of these cells, which may allow the development of long-term cell-mediated anti-tumor immunity. However, T cells have been shown to undergo metabolic exhaustion in tumor microenvironment (TME) as it poses several obstacles to their function. Applications of several mechanistic solutions to improve the efficacy of T cell-based therapies including chimeric antigen receptor (CAR) T cell therapy are yet to be determined. Modifying the metabolic properties of these cells and employing them in cancer immunotherapy is a potential strategy for improving their anti-tumor activity and therapeutic efficacy. To give an insight, in this review paper, we endeavoured to cover metabolic reprogramming in cancer and T cells, signalling mechanisms involved in immuno-metabolic regulation, the effects of the TME on T cell metabolic fitness, and targeting metabolic reprogramming of T cells for an enhanced anti-tumor response.

Keywords: T-cell, cancer, immunotherapy, metabolic reprogramming

Introduction

Cancer immunotherapy is defined as therapeutic technique that use the immune system in defense against cancers.[1] Modification of T cell-based anti-tumor immune responses is one of the approaches of cancer immunotherapy,[2] because due to the presence of unique mutations or protein expression patterns, tumor cells may be recognized and eliminated by T cells with a high degree of specificity.[1,3,4]

T cells, a type of adaptive immune response cells responsible for cell-mediated immunity, have long been recognized as key regulators of immune-mediated anti-tumor immunity. Changes in cell metabolism have been shown to enhance or suppress diverse T cell activities.[5] Naive T cells have low metabolic requirements and oxidative phosphorylation (OXPHOS) is their main source of energy.[6] However, upon antigen encounter, T cell receptor (TCR)-mediated signalling will be activated and this, in turn, induces changes in T cells' metabolism that causes an increase in proliferation and differentiation of these cells into effector T cells (Teff).[7] Activation of naive T cells enhances the up-regulation of glucose and amino acid transporters at their surface and leads to metabolic reprogramming of these cells from OXPHOS to glycolysis.[8,9]

T cells have been shown to undergo metabolic exhaustion in TME.[10] Thus, mechanistic understanding of tumor-specific T lymphocytes metabolic reprogramming may provide an important therapeutic approach along with immunotherapy methods.[11] It has been demonstrated that modulation of T cell metabolism can be a potential therapeutic target to inhibit or enhance immune responses including anti-tumor responses.[12] This review paper focuses on targeting metabolic reprogramming of T cells for enhanced anti-tumor response in cancer immunotherapy.

Received: 8 March 2022
Accepted: 5 May 2022
Published: 9 May 2022

Metabolic Reprogramming in Cancer and T Cells

Metabolic Reprogramming in Cancer Cells

Because of metabolic reprogramming, cancer cells' metabolic properties, as well as the pathways by which they acquire and refill their metabolic demands, differ from those of normal cells.[13] Under normoxic conditions, non-malignant (quiescent) cells rely on OXPHOS as their primary source of energy.[6] Unlike normal cells, cancer cells generate energy primarily through increased glycolysis in the cytosol, even under aerobic conditions. This metabolic shift of cancer cells to aerobic glycolysis is often known as the Warburg effect in recognition of Otto Warburg who originally discovered it in 1926.[14]

The difference in cancer cell metabolism from normal cells is a result of disruption of intracellular signalling pathways caused by mutated oncogenes and tumor-suppressor genes.[15] Among oncogenic mutations, alterations in the phosphoinositide 3-kinase (PI3K) pathway has repeatedly been demonstrated to be altered, and consequently plays a significant role in tumor proliferation and survival in a wide range of human malignancies.[16] When activated, the PI3K pathway induces a glycolytic phenotype in tumors and increases ATP generation via its downstream effector, Protein kinase B also known as Akt1, ensuring that cells have the bioenergetics capacity to respond to growth signals.[17,18] The PI3K enzyme itself inhibits the tumor suppressor PTEN and its loss enhances glycolysis via Akt and hypoxia-inducible factor 1-alpha (HIF-1) activation.[17] Akt promotes glycolysis by boosting the expression and membrane translocation of glucose transporters, as well as by phosphorylating glycolytic enzymes including hexokinase (HK) and phosphofructokinase (PFK).[17,19]

Furthermore, even under normoxic settings, Akt1 substantially promotes the mammalian target of rapamycin (mTOR) signalling pathway by causing inhibitory phosphorylation of tuberous sclerosis 2 (TSC2), a negative regulator of mTOR,[16,19] which indirectly influences other metabolic pathways by activating HIF-1.[19]

In addition to its role in cell cycle control and cell death,[20] p53 inhibits glycolysis[21] by increasing the production of tumor protein 53 (TP53)-induced glycolysis and apoptosis regulator (TIGAR), an enzyme that reduces levels of the glycolytic activator fructose-2,6-bisphosphate.[22] Furthermore, p53 promotes the expression of PTEN, which inhibits the PI3K pathway and hence suppress glycolysis.[23] Moreover, p53 enhances OXPHOS by increasing the expression of cytochrome C oxidase assembly protein (SCO2), which is essential for the assembly of the electron transport chain's cytochrome C oxidase complex.[21] Hence, loss of p53 shifts metabolism from OXPHOS towards glycolysis.

c-Myc is a transcription factor that promotes the expression of genes that encode glucose transporters and enzymes involved in glycolysis that includes: HK, phosphoglucose isomerase, phosphofructokinase, glyceraldehyde-3-phosphate dehydrogenase, phosphoglycerate kinase, and enolase.[24] Tumor cells that overexpress c-Myc have enhanced metabolic flux,[25] which compensates for the low efficiency of ATP synthesis via glycolysis. This occurs because increased expression of glucose transporters, such as Glucose transporter (GLUT1) 1[26] and GLUT4,[27] leads to higher glucose uptake in cancer cells.

In addition to glucose, cancer cells also rely on glutamine to fuel their metabolic need. Through glutaminolysis, glutamine is catabolized to glutamate, α-ketoglutarate which further fuels the TCA cycle of tumor cells. Furthermore, the intermediates of TCA cycles could be used for the synthesis of lipid, cholesterol, amino acids, and other essential metabolites.[28–30] Supporting their high need for nucleotides and other materials for biosynthesis due to increased proliferation of cancer cells demand for Pentose Phosphate Pathway (PPP) is important and frequently upregulated in many types of tumors.[29,31]

Aside from the classic Warburg effect in cancer cells, evidence of mutations in genes encoding for Krebs cycle enzymes, as well as the emerging paradigm of Oncometabolites-Driven Tumorigenesis, bolstered the role of metabolic change in cancer cell development.[32–35] The presence of oncogenic transformation in metabolic enzymes, as well as the metabolic difference between tumor and normal cells, suggests that a novel anticancer strategy targeting cancer cell metabolism could be developed.

Metabolic Reprogramming in T Cells

In a naive state, T cells rely primarily on the use of small amounts of nutrients such as glucose, fatty acids, and amino acids, as well as the oxidation of pyruvate and glutamine via the tri-carboxylic acid (TCA) cycle. TCR-mediated activation and T helper (Th) lineage differentiation are intricately linked to metabolic reprogramming, a shift in cellular metabolic processes.[36]

Different T cell subsets have distinct metabolic properties. Basically, compared to activated T cells, the circulating naive T cells are quiescent and their metabolic demand is primarily mediated by OXPHOS.[6] Naive T cells require cell extrinsic signals such as Interleukin (IL)-7 to maintain their basal energy-generating metabolism and to support their continued migration through secondary lymphoid tissues and immune surveillance.[9] Antigen recognition in the context of the major histocompatibility complex, together with appropriate co-stimulation, causes naive T cells to escape quiescence, become highly proliferative and differentiate into Teff that exerts their function as a cluster of differentiation (CD) 4+Th cells, such as Th1, Th2 or Th17 or as CD8+ cytotoxic T lymphocyte (CTL). T cells expand in size and undergo a metabolic shift from OXPHOS to glycolysis when activated.[37,38]

In addition to the transition to glycolysis, T-cell activation alters several metabolic processes including reduced fatty acid oxidation, decreased pyruvate flux into the TCA cycle, increased glucose flux into the PPP, and enhanced glutamine metabolism.[39–41] It has been previously evidenced that glutamine uptake and metabolism is indispensable for the functional aspect of T cells.[42]

After the antigen is cleared through several T cell responses, most Teff cells die and a small population of antigen-specific T cells that survive become T memory cells (Tm). Tm, unlike Teff, does not grow fast and as a result, they do not require a high rate of anabolic metabolism. Instead, they produce energy to aid in self-renewal.[8,12]

Tm cells have an increased mitochondrial mass and consequently a higher mitochondrial spare respiratory capacity (SRC), which is the maximum mitochondrial respiratory capacity available to a cell to produce energy under conditions of increased effort or stress.[9,43,44] Tm cells rely on β-oxidation of de novo generated fatty acids that have been synthesized from glucose during the effector phase by fatty acid synthesis and stored intracellularly for energy generation, rather than uptake and use of extracellular lipids.[45] On the other hand, FAO and other ATP-generating catabolic pathways are actively suppressed in Teff cells. In general, the metabolism-cell fate connection has been demonstrated with the switch to glycolysis that occurs with Teff differentiation and the switch to FAO that occurs with Teff to Tm conversion.[46] Moreover, conversion toward a T regulatory (Treg) phenotype is also favored in conditions of increased OXPHOS and decreased glycolysis.[47]

Signalling Pathways Involved in Immunometabolic Regulation

The activation of various metabolic pathways has a significant impact on cell differentiation and function. Metabolic reprogramming is influenced by key receptor signalling events, growth factor cytokines, and nutrient availability.[8] Understanding how specific cellular signalling pathways involved in immunometabolic regulation may uncover therapeutic targets to modulate metabolic programming and T cell responses that can lead to new cancer therapies.

PI3K Signalling Pathway

The PI3K signalling system regulates cell survival, growth, metabolism, and glucose homeostasis.[16] The PI3K family consists of three classes including class I, class II, and class III.[48] Class 1 PI3K, lipid kinases that phosphorylate phosphatidylinositol-(4,5)-bisphosphate [PI(4,5)P2] to generate the lipid signalling molecule phosphatidylinositol-(3,4,5)-triphosphate [PI(3,4,5)P3], play a crucial role in many aspects of T cell function.[49]

TCR, CD 28, and Interleukin 2 receptor (IL-2R) activation phosphorylate and activates PI3K while inactivating PI3K-suppressing molecules including PTEN and PIK3IP1. PI3K activity converts PIP2 to PIP3, and PIP3 assists in the recruitment and activation of downstream signalling molecules such as pyruvate dehydrogenase kinase 1(PDK1) and Akt. mTORC2 further activates Akt, enabling increased metabolism and T cell effector activity.[50]

mTOR Signaling Pathway

Signals from the TCR, costimulatory molecules, and growth factor cytokines activate signaling pathways that enhance transcriptional programs required for effector actions. These signals also activate the kinase mTOR, which causes glycolysis induction across numerous routes to support cell growth, proliferation, and function.[51]

mTOR, a serine/threonine-protein kinase, plays an important role in metabolism control by recognizing and integrating signals in response to nutrients, growth factors, energy, and stress.[52] It exists in two different complexes: mTOR complex 1(mTORC 1) and mTOR complex 2 (mTORC2).[53] T cell fate decisions are determined by the interaction

of mTOR and metabolism.[54] mTOR signaling is required for the generation of CD4+ effector T cells, as mTOR-deficient T cells fail to differentiate into Th1, Th2, and Th17 cells both in vitro and in vivo. T cells lacking in mTOR, on the other hand, evolve into Treg cells.[55] mTORC1 signals govern Th1 and Th17 lineage differentiation, whereas mTORC2 signals promote Th2 development.[56]

The mTORC1 signaling pathway promotes metabolic reprogramming toward enhanced aerobic glycolysis, glutaminolysis, and mitochondrial metabolism remodeling.[57] mTORC2 activity is also linked to metabolic reprogramming by regulating the activation of AGC kinases, however, its function appears to be less critical for early metabolic programming (ie, that occurs during first quiescence exit) that promotes T cell activation.[58]

mTOR is a crucial regulator of translation[59] and cell growth[60] that drives glycolysis and cellular metabolism[61] by raising glycolytic enzyme activity and increasing the expression of nutrient transporters. Interestingly, activated Akt stimulates the mTOR pathway, allowing for greater consumption of glucose and amino acids.[17,30,62] mTOR activation increases the expression of GLUT11[63] and transgenic expression of GLUT1 increases T cell proliferation and cytokine production.[64] Increased glycolysis and glucose absorption are linked to the enhanced effector actions that occur upon T cell activation.[65]

mTOR activation and glycolysis activation result in the production of downstream transcriptional regulators such as HIF-1α, c-Myc, and estrogen-related receptor alpha (ERRα), which regulate metabolism in T cells and activate pathways involved in rapid cell proliferation and effector function.[66] The HIF-1α-dependent transcriptional pathway promotes glycolysis in T cells and promotes the development of the TH17 fraction while suppressing regulatory T cells (Treg).[47] When c-Myc is activated, enzymes involved in glycolysis and glutaminolysis are expressed, the results of which contribute to the production of lipids, amino acids, and nucleic acids for cellular expansion.[41] ERRα functions as a metabolic regulator of effector CD4+ T-cell homeostasis and function by influencing metabolic gene expression and glucose metabolism in a wide range of ways.[67]

In addition to transcriptional regulation, post-translational modulation of glucose uptake and glycolysis is essential for T cell effector function development. The PI3K/mTOR pathway, in particular, plays an important role in promoting the glucose metabolism required for effector T cell differentiation while inhibiting Treg generation.[52,68] mTOR signaling also has pleiotropic effects on mitochondrial metabolism. In naive T cells, mitochondrial metabolism is catabolic, which supports cellular homeostasis, and mTOR signaling is actively retained at lower levels, establishing these cells' quiescence.[69] The up-regulation of mitochondrial metabolism by mTORC1 enhances efficient OXPHOS as well as the production of many epigenetic-regulating metabolites to modulate T cell functional programming.[70–72]

LKB1–AMPK Signaling Pathway

Liver kinase B1 (LKB1) and Adenosine monophosphate(AMP) activated protein kinase (AMPK) contribute to T cell development and function through regulating metabolic reprogramming.[50] The LKB1-AMPK signaling pathway regulates cellular metabolism, growth, and survival in response to changes in nutrient and energy needs. It also stimulates catabolic pathways that generate ATP and allow metabolic reprogramming in T cells. AMPK promotes T cell survival by enhancing glutaminolysis and mitochondrial OXPHOS in maintaining intracellular ATP levels in the absence of glucose through promoting the expression of glutamine uptake and metabolism genes.[73]

Increased intracellular AMP-to-ATP concentrations activate the energy stress sensor AMPK, which promotes FAO.[62] AMPK is required for the production of Tm; permits effector T cells to physiologically adjust to nutritional stress; and controls T cell effector function via mTOR inhibition.[73,74]

Activated T cells were discovered to have a glucose-sensitive metabolic checkpoint regulated by the energy sensor AMPK that regulated mRNA translation and glutamine-dependent mitochondrial metabolism to maintain T cell bioenergetics and viability, implying that AMPK-dependent regulation of metabolic homeostasis is a key regulator of T cell-mediated adaptive immunity.

Effects of Tumor Microenvironment on T Cell Metabolic Fitness

Cancer cells, stromal tissue and the extracellular matrix (ECM) that surrounds it all make up a complex milieu called TME.[75] The TME is regarded as a critical component of cancer initiation and spread. The TME's intricacy is considered

to be related to uncontrolled cancer cell growth and faulty blood vessel formation.[76] According to studies, the TME is distinguished by acidic pH conditions, hypoxia, endogenous H_2O_2, and changes in the expression of ECM proteins, all of which play important roles in tumor development and cancer metabolism.[77,78]

The acidic pH is produced by membrane proteins such as ATPase, monocarboxylate transporter 1 (MCT1) and MCT4 excreting protons (H+) and lactate during anaerobic glycolysis.[79] Acidic pH promotes cancer cell migration and invasion by increasing the production of angiogenic molecules such as vascular endothelial growth factor A (VEGFA) and IL-8.[79] Hypoxia (partial oxygen pressure of 10 mmHg) has been observed in a number of solid tumors.[80,81]

Cancer cells' high metabolic activity, along with a weak vascular blood supply in the TME, might cause nutritional deficiency.[82] These TME circumstances can affect TCR signaling, glycolytic metabolism, amino acid absorption, and metabolism, all of which are characteristics of Teff, leading to decreased anti-tumor effector activities of tumor-specific T cells. Treg cells, on the other hand, which rely mostly on FAO,[9,63,81] may survive in these circumstances and exert inhibitory effects on tumor-specific Teff. The activation of AMPK, is also connected to the expansion of Treg cells in the TME.[73]

Waste produced by hypermetabolic cancer cells, such as lactate and amino acid metabolic products such as kynurenine, can limit T cell activation and cytolytic activity while supporting Treg differentiation.[6,83] HIF1, which is activated by TME hypoxia, can also enhance the formation and maintenance of Treg cells.[84] Hypoxia-induced (HIF1) promotes programmed death-ligand 1 (PD-L1) expression in myeloid-derived suppressor cells (MDSC), resulting in strong immunosuppressive effects in tumor-specific Teff cells.[85]

T cell "metabolic fitness" is critical for efficient antitumor immunity, but it is hampered by the tumor nutritional microenvironment's specific circumstances of restricted food supply and the impact of immunological checkpoints.[86] T cells develop an "exhausted" phenotype inside the immune-suppressive tumor milieu, which is characterized by gradual loss of effector activities, changes in the expression and function of critical transcription factors.[10]

Furthermore, "exhausted" T cells exhibit a persistent overexpression and co-expression of numerous inhibitory receptors, which can have significant effects on T cell activity.[87,88] T cell exhaustion is characterized by reduced glycolysis and OXPHOS and indications of mitochondrial dysfunction.[88–90] Lower levels of glycolysis have been linked to decreased GLUT1 expression, lower phosphoenolpyruvate (PEP) levels in T cells and glucose concentrations in the TME.[91–94]

Signaling through the TCR and the costimulatory protein CD28 activates the PI3K-AKT-mTOR pathway, resulting in enhanced aerobic glycolysis and OXPHOS during a normal immunological response that culminates in antigen clearance.[95] CD28 costimulation during activation is also crucial in boosting mitochondrial biogenesis and, as a result, sparing respiratory capacity in Teff cells transitioning to the Tm state.[96] However, the inhibitory molecule PD-1 is constitutively high in exhausted T cells, inhibiting CD28 signaling and CD28-dependent metabolic activities.[97,98] Thus, identifying different bioenergetics patterns in exhausted T cell subsets might give new methods for determining the amount of T cell exhaustion as well as uncover novel targets for reversing depletion.

Modulation of T Cells Metabolism for Enhanced Anti-Tumor Response

Recent advances in cancer biology shed more definitive light on the therapeutic use of immune cells for efficient antitumor immune response. This includes tumor-infiltrating lymphocytes (TILs) and the latest CAR T cell therapy. Although immunotherapy has been increasingly shown wonderful clinical outcomes in patients with Leukemia, and other cancer types, there are still challenges related to specificity, and side effects possibly of life-threatening immune-related toxicities.[99,100] This could be associated with TME that creates many impediments to immune cell activity, including a metabolically demanding and immunosuppressive milieu.[75,78]

Cellular metabolic pathways have been demonstrated to play critical roles in controlling T cell fate, function, and longevity.[101] And regulation of T cell metabolism has been investigated as a possible therapeutic target for enhancing or suppressing immunological responses in a variety of situations, including anti-tumor immunity.[102] Modifying the metabolic characteristics of T cells used in cancer immunotherapy is therefore a viable method for enhancing anti-tumor activity and therapeutic effectiveness.[12]

CRISPR/Cas9 genome editing technology has been applied to enhance T cell effector function for therapeutic applications.[103] Regulating cell metabolism to improve CAR T cell activity is an essential modulation method for better immunotherapy against cancer.[104] Because T cells are controlled by metabolic molecules such as Diacylglycerol Kinases (DGKs), a class of enzymes that catabolize diacylglycerols (DAGs),[105] using CRISPR/Cas9 genome editing to knock out DGK isoforms increases TCR signalling in CAR T cells.[106] Furthermore, Kawalekar et al show that CAR T cells engineered to express 4-1BB signaling domains have increased in vitro persistence, central memory differentiation, and mitochondrial biogenesis,[107] all of which play a role in enhancing the anti-tumor response of metabolically reprogrammed T cells.

The production of tumor-specific Tm cells in conjunction with the generation of Teff cells is a primary objective of new immunomodulatory methods. Instead of a transitory anti-tumor impact, this will allow for persistent immune-mediated anti-tumor action. One approach is drug repositioning (DR), which involves searching for anti-cancer therapeutic effects in commonly prescribed drugs for non-malignant diseases because the safety and frequency of adverse effects of these treatments have previously been established.[108]

Metformin is a commonly used and well-tolerated medication for the treatment of type 2 diabetes mellitus (T2DM),[109] and it has been demonstrated to have anti-tumor properties through a variety of mechanisms.[46,110–112] Metformin has been shown in studies to influence Teff cells and increase the formation of Tm cells via AMPK activation.[46,63] Eikawa et al discovered that metformin can protect $CD8^+$ T cells from eventual functional depletion and death, as well as enhance T cell functioning in the TME.[113] This may also assist exhausted T cells in regaining function. In addition, mTOR inhibitors such as rapamycin can have metabolism-targeting effects on T cells, through increasing memory $CD8^+$ T cell production.[114,115]

The longevity and durability of T cells used in immunotherapy are likely to be key factors in determining treatment effectiveness. Geiger et al demonstrated that higher L-arginine levels can have a pleiotropic influence on T cell activation, differentiation, and function, ranging from enhanced bioenergetics and survival to anti-tumor efficacy in vivo.[5] Increased L-arginine levels may upregulate the serine biosynthesis pathway, which has been demonstrated to feed the TCA cycle and, as a result, OXPHOS.[116]

Another study conducted by Jaccard et al indicates that pharmacological suppression of the metabolic enzyme isocitrate dehydrogenase 2 (IDH2) during $CD8^+$ T cell priming resulted in greater memory formation and tumor growth inhibition upon adoptive cellular therapy (ACT) into melanoma tumor-bearing mice.[117]

In addition, manipulation of cellular fatty acid metabolism may potentially be of therapeutic relevance, since changes in basic cellular lipid metabolism can have a major impact on T cell destiny and function.[118] Fatty acid synthesis (FAS) promotes the proliferation and differentiation of Teff cells in response to stimulation, whereas FAO is required for the formation of $CD8^+$ T cell memory cells.[45] Kim et al were able to provide evidence on activation of anticancer effector functions of T cells through nanoparticle-induced lipid metabolic reprogramming.[119]

Metabolic pathways or enzymes that specifically inhibit cancer cell growth while enhancing anti-tumor T cell function can be targeted. Leone et al show that inhibiting glutamine metabolism in tumor-bearing mice suppresses cancer cell oxidative and glycolytic metabolism, resulting in decreased hypoxia, acidosis, and nutrient depletion, whereas Teff cells responded to glutamine antagonism by significantly up-regulating oxidative metabolism and adopting a long-lived, highly activated phenotype, allowing restoration of antitumor immunity.[120] It has been demonstrated that inhibiting cancer cell glycolysis preserves antitumor T-cell function and improves response to checkpoint immunotherapy.[121]

Conclusion and Future Perspectives

To adapt to changing extracellular and intracellular circumstances, T cells undergo metabolic reprogramming. The presence of intense nutritional competition between cancer and T cells inside the tumor microenvironment causes T cells to exhaust, resulting in diminished antitumor responses. Several studies have shown that metabolic reprogramming plays an important role in supporting the transition from a resting to an active state, as well as how numerous signalling pathways are involved in immunometabolic regulation and therefore T cell functions.

As a result, mechanistic knowledge of such immunometabolic alterations allows for the identification of novel therapeutic targets to enhance T cell immunological activity. The synergistic effects of repurposed medications that target

metabolic pathways, such as metformin, with established anti-cancer immunotherapies should be studied in clinical trials to aid in the development of novel treatments. Future research should focus on developing a strategy that can halt cancer cell growth while improving anti-tumor T cell function by targeting metabolic enzymes. Furthermore, metabolic programs that can boost anti-tumor activity should be included in CAR T cell design.

Abbreviations

ACT, Adoptive cell therapy; AMPK, AMP-activated kinase; ATP, Adenosine triphosphate; CAR, Chimeric antigen receptor; CD, Cluster of differentiation; DAGs, diacylglycerols; DGKs, Diacylglycerol Kinases; ERRa, Estrogen-related receptor alpha; FAO, Fatty acid oxidation; FAS, Fatty acid Synthesis; FOXO, Fork head box subfamily O; GLS, Glutaminase; Glut, Glucose transporter; HIF-1 α, Hypoxia-inducible factor 1-alpha; HK, Hexokinase; IDH2, isocitrate dehydrogenase 2; IL, Interleukin; LKB1–AMPK, Liver kinase B1–5′ AMP-activated protein kinase; MCT, Monocarboxylate transporter; MDSC, Myeloid-derived suppressor cells; mTOR, Mammalian target of rapamycin; mTORC, mTOR complex; NADPH, Nicotinamide adenine dinucleotide phosphate; OXPHOS, Oxidative phosphorylation; PD1, Programmed cell death protein 1; PEP, Phosphoenolpyruvate; PFK, Phosphofructokinase; PI3K, Phosphoinositide 3-kinases; PPP, Pentose Phosphate Pathway; PTEN, Phosphatase and tensin homolog; SCO2, Synthesis of cytochrome c oxidase 2; SRC, Spare respiratory capacity; T2DM, Type 2 diabetes mellitus; TCA, Tricarboxylic acid; TCR, T cell receptor; Teff, Effector T cells; Th, T helper; TILs, Tumor-infiltrating lymphocytes; TIGAR, TP53-induced glycolysis and apoptosis regulator; Tm, T memory cells; TME, Tumor microenvironment; Treg, T regulatory; TSC2, Tuberous sclerosis 2; VEGFA, Vascular endothelial growth factor A.

Disclosure

We declare absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Rosenberg SA, Restifo NP. Adoptive cell transfer as personalized immunotherapy for human cancer. *Science*. 2015;348(6230):62–68. doi:10.1126/science.aaa4967
2. Rosenberg SA. Raising the bar: the curative potential of human cancer immunotherapy. *Sci Transl Med*. 2012;4(127):127ps8–ps8. doi:10.1126/scitranslmed.3003634
3. Wang HY, Peng G, Guo Z, Shevach EM, Wang R-F. Recognition of a new ARTC1 peptide ligand uniquely expressed in tumor cells by antigen-specific CD4+ regulatory T cells. *J Immunol*. 2005;174(5):2661–2670. doi:10.4049/jimmunol.174.5.2661
4. Lim WA, June CH. The principles of engineering immune cells to treat cancer. *Cell*. 2017;168(4):724–740. doi:10.1016/j.cell.2017.01.016
5. Geiger R, Rieckmann JC, Wolf T, et al. L-arginine modulates T cell metabolism and enhances survival and anti-tumor activity. *Cell*. 2016;167(3):829–42. e13. doi:10.1016/j.cell.2016.09.031
6. Herbel C, Patsoukis N, Bardhan K, Seth P, Weaver JD, Boussiotis VA. Clinical significance of T cell metabolic reprogramming in cancer. *Clin Transl Med*. 2016;5(1):1–23. doi:10.1186/s40169-016-0110-9
7. Courtney AH, Lo W-L, Weiss A. TCR signaling: mechanisms of initiation and propagation. *Trends Biochem Sci*. 2018;43(2):108–123. doi:10.1016/j.tibs.2017.11.008
8. Buck MD, O'sullivan D, Pearce EL. T cell metabolism drives immunity. *J Exp Med*. 2015;212(9):1345–1360. doi:10.1084/jem.20151159
9. MacIver NJ, Michalek RD, Rathmell JC. Metabolic regulation of T lymphocytes. *Annu Rev Immunol*. 2013;31(1):259–283. doi:10.1146/annurev-immunol-032712-095956
10. O'Connell P, Hyslop S, Blake MK, Godbehere S, Amalfitano A, Aldhamen YA. SLAMF7 signaling reprograms T cells toward exhaustion in the tumor microenvironment. *J Immunol*. 2021;206(1):193–205. doi:10.4049/jimmunol.2000300
11. Zhang L, Romero P. Metabolic control of CD8+ T cell fate decisions and antitumor immunity. *Trends Mol Med*. 2018;24(1):30–48. doi:10.1016/j.molmed.2017.11.005
12. O'Sullivan D, Pearce EL. Targeting T cell metabolism for therapy. *Trends Immunol*. 2015;36(2):71–80. doi:10.1016/j.it.2014.12.004
13. Ward PS, Thompson CB. Metabolic reprogramming: a cancer hallmark even Warburg did not anticipate. *Cancer Cell*. 2012;21(3):297–308.
14. Warburg O. On the origin of cancer cells. *Science*. 1956;123(3191):309–314. doi:10.1126/science.123.3191.309
15. Vogelstein B, Kinzler KW. Cancer genes and the pathways they control. *Nat Med*. 2004;10(8):789–799. doi:10.1038/nm1087
16. Engelman JA, Luo J, Cantley LC. The evolution of phosphatidylinositol 3-kinases as regulators of growth and metabolism. *Nat Rev Genet*. 2006;7(8):606–619. doi:10.1038/nrg1879
17. Elstrom RL, Bauer DE, Buzzai M, et al. Akt stimulates aerobic glycolysis in cancer cells. *Cancer Res*. 2004;64(11):3892–3899. doi:10.1158/0008-5472.CAN-03-2904
18. Fan Y, Dickman KG, Zong W-X. Akt and c-Myc differentially activate cellular metabolic programs and prime cells to bioenergetic inhibition. *J Biol Chem*. 2010;285(10):7324–7333. doi:10.1074/jbc.M109.035584
19. Robey RB, Hay N. Is Akt the "Warburg kinase"?—Akt-energy metabolism interactions and oncogenesis. *Semin Cancer Biol*. 2009;19(1):25–31. doi:10.1016/j.semcancer.2008.11.010

20. Sengupta S, Harris CC. p53: traffic cop at the crossroads of DNA repair and recombination. *Nat Rev Mol Cell Biol*. 2005;6(1):44–55. doi:10.1038/nrm1546
21. Matoba S, Kang J-G, Patino WD, et al. p53 regulates mitochondrial respiration. *Science*. 2006;312(5780):1650–1653. doi:10.1126/science.1126863
22. Bensaad K, Tsuruta A, Selak MA, et al. TIGAR, a p53-inducible regulator of glycolysis and apoptosis. *Cell*. 2006;126(1):107–120. doi:10.1016/j.cell.2006.05.036
23. Stambolic V, MacPherson D, Sas D, et al. Regulation of PTEN transcription by p53. *Mol Cell*. 2001;8(2):317–325. doi:10.1016/S1097-2765(01)00323-9
24. Osthus RC, Shim H, Kim S, et al. Deregulation of glucose transporter 1 and glycolytic gene expression by c-Myc. *J Biol Chem*. 2000;275(29):21797–21800. doi:10.1074/jbc.C000023200
25. Le A, Lane AN, Hamaker M, et al. Glucose-independent glutamine metabolism via TCA cycling for proliferation and survival in B cells. *Cell Metab*. 2012;15(1):110–121. doi:10.1016/j.cmet.2011.12.009
26. Young CD, Lewis AS, Rudolph MC, et al. Modulation of glucose transporter 1 (GLUT1) expression levels alters mouse mammary tumor cell growth in vitro and in vivo. *PLoS One*. 2011;6(8):e23205. doi:10.1371/journal.pone.0023205
27. Huang S, Czech MP. The GLUT4 glucose transporter. *Cell Metab*. 2007;5(4):237–252. doi:10.1016/j.cmet.2007.03.006
28. Dang CV. Glutaminolysis: supplying carbon or nitrogen or both for cancer cells? *Cell Cycle*. 2010;9(19):3884–3886. doi:10.4161/cc.9.19.13302
29. DeBerardinis RJ, Lum JJ, Hatzivassiliou G, Thompson CB. The biology of cancer: metabolic reprogramming fuels cell growth and proliferation. *Cell Metab*. 2008;7(1):11–20. doi:10.1016/j.cmet.2007.10.002
30. DeBerardinis RJ, Sayed N, Ditsworth D, Thompson CB. Brick by brick: metabolism and tumor cell growth. *Curr Opin Genet Dev*. 2008;18(1):54–61. doi:10.1016/j.gde.2008.02.003
31. Riganti C, Gazzano E, Polimeni M, Aldieri E, Ghigo D. The pentose phosphate pathway: an antioxidant defense and a crossroad in tumor cell fate. *Free Radic Biol Med*. 2012;53(3):421–436. doi:10.1016/j.freeradbiomed.2012.05.006
32. Aghili M, Zahedi F, Rafiee E. Hydroxyglutaric aciduria and malignant brain tumor: a case report and literature review. *J Neurooncol*. 2009;91(2):233–236. doi:10.1007/s11060-008-9706-2
33. Baysal BE. A recurrent stop-codon mutation in succinate dehydrogenase subunit B gene in normal peripheral blood and childhood T-cell acute leukemia. *PLoS One*. 2007;2(5):e436. doi:10.1371/journal.pone.0000436
34. Green A, Beer P. Somatic mutations of IDH1 and IDH2 in the leukemic transformation of myeloproliferative neoplasms. *N Engl J Med*. 2010;362(4):369–370. doi:10.1056/NEJMc0910063
35. Van Vranken JG, Na U, Winge DR, Rutter J. Protein-mediated assembly of succinate dehydrogenase and its cofactors. *Crit Rev Biochem Mol Biol*. 2015;50(2):168–180. doi:10.3109/10409238.2014.990556
36. Almeida L, Lochner M, Berod L, Sparwasser T. Metabolic pathways in T cell activation and lineage differentiation. *Semin Immunol*. 2016;28(5):514–524. doi:10.1016/j.smim.2016.10.009
37. Krauss S, Brand MD, Buttgereit F. Signaling takes a breath–new quantitative perspectives on bioenergetics and signal transduction. *Immunity*. 2001;15(4):497–502. doi:10.1016/S1074-7613(01)00205-9
38. Rathmell JC, Vander Heiden MG, Harris MH, Frauwirth KA, Thompson CB. In the absence of extrinsic signals, nutrient utilization by lymphocytes is insufficient to maintain either cell size or viability. *Mol Cell*. 2000;6(3):683–692. doi:10.1016/S1097-2765(00)00066-6
39. Newsholme E, Crabtree B, Ardawi M. The role of high rates of glycolysis and glutamine utilization in rapidly dividing cells. *Biosci Rep*. 1985;5(5):393–400. doi:10.1007/BF01116556
40. Newsholme EA, Crabtree B, Ardawi MSM. Glutamine metabolism in lymphocytes: its biochemical, physiological and clinical importance. *Q J Exp Physiol*. 1985;70(4):473–489. doi:10.1113/expphysiol.1985.sp002935
41. Wang R, Dillon CP, Shi LZ, et al. The transcription factor Myc controls metabolic reprogramming upon T lymphocyte activation. *Immunity*. 2011;35(6):871–882. doi:10.1016/j.immuni.2011.09.021
42. Carr EL, Kelman A, Wu GS, et al. Glutamine uptake and metabolism are coordinately regulated by ERK/MAPK during T lymphocyte activation. *J Immunol*. 2010;185(2):1037–1044. doi:10.4049/jimmunol.0903586
43. Gubser PM, Bantug GR, Razik L, et al. Rapid effector function of memory CD8+ T cells requires an immediate-early glycolytic switch. *Nat Immunol*. 2013;14(10):1064–1072. doi:10.1038/ni.2687
44. van der Windt GJ, Everts B, Chang C-H, et al. Mitochondrial respiratory capacity is a critical regulator of CD8+ T cell memory development. *Immunity*. 2012;36(1):68–78. doi:10.1016/j.immuni.2011.12.007
45. O'Sullivan D, van der Windt GJ, Huang S-C-C, et al. Memory CD8+ T cells use cell-intrinsic lipolysis to support the metabolic programming necessary for development. *Immunity*. 2014;41(1):75–88. doi:10.1016/j.immuni.2014.06.005
46. Pearce EL, Walsh MC, Cejas PJ, et al. Enhancing CD8 T-cell memory by modulating fatty acid metabolism. *Nature*. 2009;460(7251):103–107. doi:10.1038/nature08097
47. Shi LZ, Wang R, Huang G, et al. HIF1α–dependent glycolytic pathway orchestrates a metabolic checkpoint for the differentiation of TH17 and Treg cells. *J Exp Med*. 2011;208(7):1367–1376. doi:10.1084/jem.20110278
48. Vanhaesebroeck B, Leevers SJ, Panayotou G, Waterfield MD. Phosphoinositide 3-kinases: a conserved family of signal transducers. *Trends Biochem Sci*. 1997;22(7):267–272. doi:10.1016/S0968-0004(97)01061-X
49. Okkenhaug K, Vanhaesebroeck B. PI3K in lymphocyte development, differentiation and activation. *Nat Rev Immunol*. 2003;3(4):317–330. doi:10.1038/nri1056
50. Saravia J, Raynor JL, Chapman NM, Lim SA, Chi H. Signaling networks in immunometabolism. *Cell Res*. 2020;30(4):328–342. doi:10.1038/s41422-020-0301-1
51. Waickman AT, Powell JD. mTOR, metabolism, and the regulation of T-cell differentiation and function. *Immunol Rev*. 2012;249(1):43–58. doi:10.1111/j.1600-065X.2012.01152.x
52. Powell JD, Pollizzi KN, Heikamp EB, Horton MR. Regulation of immune responses by mTOR. *Annu Rev Immunol*. 2012;30(1):39–68. doi:10.1146/annurev-immunol-020711-075024
53. Laplante M, Sabatini DM. mTOR signaling at a glance. *J Cell Sci*. 2009;122(20):3589–3594. doi:10.1242/jcs.051011

54. Yang K, Chi H. mTOR and metabolic pathways in T cell quiescence and functional activation. *Semin Immunol*. 2012;24(6):421–428. doi:10.1016/j.smim.2012.12.004
55. Delgoffe GM, Kole TP, Zheng Y, et al. The mTOR kinase differentially regulates effector and regulatory T cell lineage commitment. *Immunity*. 2009;30(6):832–844.
56. Delgoffe GM, Pollizzi KN, Waickman AT, et al. The kinase mTOR regulates the differentiation of helper T cells through the selective activation of signaling by mTORC1 and mTORC2. *Nat Immunol*. 2011;12(4):295–303. doi:10.1038/ni.2005
57. Chapman NM, Boothby MR, Chi H. Metabolic coordination of T cell quiescence and activation. *Nat Rev Immunol*. 2020;20(1):55–70. doi:10.1038/s41577-019-0203-y
58. Yang K, Shrestha S, Zeng H, et al. T cell exit from quiescence and differentiation into Th2 cells depend on Raptor-mTORC1-mediated metabolic reprogramming. *Immunity*. 2013;39(6):1043–1056. doi:10.1016/j.immuni.2013.09.015
59. Gingras A-C, Raught B, Sonenberg N. mTOR signaling to translation. In: *TOR*; 2004: 169–197.
60. Kim D-H, Sarbassov DD, Ali SM, et al. mTOR interacts with raptor to form a nutrient-sensitive complex that signals to the cell growth machinery. *Cell*. 2002;110(2):163–175. doi:10.1016/S0092-8674(02)00808-5
61. Zoncu R, Efeyan A, Sabatini DM. mTOR: from growth signal integration to cancer, diabetes and ageing. *Nat Rev Mol Cell Biol*. 2011;12(1):21–35. doi:10.1038/nrm3025
62. Jones RG, Thompson CB. Revving the engine: signal transduction fuels T cell activation. *Immunity*. 2007;27(2):173–178. doi:10.1016/j.immuni.2007.07.008
63. Michalek RD, Gerriets VA, Jacobs SR, et al. Cutting edge: distinct glycolytic and lipid oxidative metabolic programs are essential for effector and regulatory CD4+ T cell subsets. *J Immunol*. 2011;186(6):3299–3303. doi:10.4049/jimmunol.1003613
64. Jacobs SR, Herman CE, MacIver NJ, et al. Glucose uptake is limiting in T cell activation and requires CD28-mediated Akt-dependent and independent pathways. *J Immunol*. 2008;180(7):4476–4486. doi:10.4049/jimmunol.180.7.4476
65. Cham CM, Gajewski TF. Glucose availability regulates IFN-γ production and p70S6 kinase activation in CD8+ effector T cells. *J Immunol*. 2005;174(8):4670–4677. doi:10.4049/jimmunol.174.8.4670
66. Doedens AL, Phan AT, Stradner MH, et al. Hypoxia-inducible factors enhance the effector responses of CD8+ T cells to persistent antigen. *Nat Immunol*. 2013;14(11):1173–1182. doi:10.1038/ni.2714
67. Michalek RD, Gerriets VA, Nichols AG, et al. Estrogen-related receptor-α is a metabolic regulator of effector T-cell activation and differentiation. *Proc Nat Acad Sci*. 2011;108(45):18348–18353. doi:10.1073/pnas.1108856108
68. Düvel K, Yecies JL, Menon S, et al. Activation of a metabolic gene regulatory network downstream of mTOR complex 1. *Mol Cell*. 2010;39(2):171–183. doi:10.1016/j.molcel.2010.06.022
69. Yang K, Neale G, Green DR, He W, Chi H. The tumor suppressor Tsc1 enforces quiescence of naive T cells to promote immune homeostasis and function. *Nat Immunol*. 2011;12(9):888–897. doi:10.1038/ni.2068
70. Chisolm DA, Savic D, Moore AJ, et al. CCCTC-binding factor translates interleukin 2-and α-ketoglutarate-sensitive metabolic changes in T cells into context-dependent gene programs. *Immunity*. 2017;47(2):251–67. e7. doi:10.1016/j.immuni.2017.07.015
71. Johnson MO, Wolf MM, Madden MZ, et al. Distinct regulation of Th17 and Th1 cell differentiation by glutaminase-dependent metabolism. *Cell*. 2018;175(7):1780–95. e19. doi:10.1016/j.cell.2018.10.001
72. Tan H, Yang K, Li Y, et al. Integrative proteomics and phosphoproteomics profiling reveals dynamic signaling networks and bioenergetics pathways underlying T cell activation. *Immunity*. 2017;46(3):488–503.
73. Blagih J, Coulombe F, Vincent EE, et al. The energy sensor AMPK regulates T cell metabolic adaptation and effector responses in vivo. *Immunity*. 2015;42(1):41–54. doi:10.1016/j.immuni.2014.12.030
74. MacIver NJ, Blagih J, Saucillo DC, et al. The liver kinase B1 is a central regulator of T cell development, activation, and metabolism. *J Immunol*. 2011;187(8):4187–4198. doi:10.4049/jimmunol.1100367
75. Binnewies M, Roberts EW, Kersten K, et al. Understanding the tumor immune microenvironment (TIME) for effective therapy. *Nat Med*. 2018;24(5):541–550. doi:10.1038/s41591-018-0014-x
76. Liu J, Chen Q, Feng L, Liu Z. Nanomedicine for tumor microenvironment modulation and cancer treatment enhancement. *Nano Today*. 2018;21:55–73. doi:10.1016/j.nantod.2018.06.008
77. Cuvier C, Jang A, Hill R. Exposure to hypoxia, glucose starvation and acidosis: effect on invasive capacity of murine tumor cells and correlation with cathepsin (L+ B) secretion. *Clin Exp Metastasis*. 1997;15(1):19–25. doi:10.1023/A:1018428105463
78. Witz IP, Levy-Nissenbaum O. The tumor microenvironment in the post-PAGET era. *Cancer Lett*. 2006;242(1):1–10. doi:10.1016/j.canlet.2005.12.005
79. Kondo A, Yamamoto S, Nakaki R, et al. Extracellular acidic pH activates the sterol regulatory element-binding protein 2 to promote tumor progression. *Cell Rep*. 2017;18(9):2228–2242. doi:10.1016/j.celrep.2017.02.006
80. Lee P, Chandel NS, Simon MC. Cellular adaptation to hypoxia through hypoxia inducible factors and beyond. *Nat Rev Mol Cell Biol*. 2020;21(5):268–283. doi:10.1038/s41580-020-0227-y
81. Swinson DE, Jones JL, Richardson D, et al. Carbonic anhydrase IX expression, a novel surrogate marker of tumor hypoxia, is associated with a poor prognosis in non-small-cell lung cancer. *J Clin Oncol*. 2003;21(3):473–482. doi:10.1200/JCO.2003.11.132
82. Le Bourgeois T, Strauss L, Aksoylar H-I, et al. Targeting T cell metabolism for improvement of cancer immunotherapy. *Front Oncol*. 2018;8:237. doi:10.3389/fonc.2018.00237
83. Siska PJ, Beckermann KE, Mason FM, et al. Mitochondrial dysregulation and glycolytic insufficiency functionally impair CD8 T cells infiltrating human renal cell carcinoma. *JCI Insight*. 2017;2(12):12. doi:10.1172/jci.insight.93411
84. Ben-Shoshan J, Maysel-Auslender S, Mor A, Keren G, George J. Hypoxia controls CD4+ CD25+ regulatory T-cell homeostasis via hypoxia-inducible factor-1α. *Eur J Immunol*. 2008;38(9):2412–2418. doi:10.1002/eji.200838318
85. Noman MZ, Desantis G, Janji B, et al. PD-L1 is a novel direct target of HIF-1α, and its blockade under hypoxia enhanced MDSC-mediated T cell activation. *J Exp Med*. 2014;211(5):781–790. doi:10.1084/jem.20131916
86. Siska PJ, Rathmell JC. T cell metabolic fitness in antitumor immunity. *Trends Immunol*. 2015;36(4):257–264. doi:10.1016/j.it.2015.02.007
87. Blackburn SD, Shin H, Freeman GJ, Wherry EJ. Selective expansion of a subset of exhausted CD8 T cells by αPD-L1 blockade. *Proc Nat Acad Sci*. 2008;105(39):15016–15021. doi:10.1073/pnas.0801497105

88. Wherry EJ, Kurachi M. Molecular and cellular insights into T cell exhaustion. *Nat Rev Immunol*. 2015;15(8):486–499. doi:10.1038/nri3862
89. Sharma S, Yang S-C, Zhu L, et al. Tumor cyclooxygenase-2/Prostaglandin E2–dependent promotion of FOXP3 expression and CD4+ CD25+ T regulatory cell activities in lung cancer. *Cancer Res*. 2005;65(12):5211–5220. doi:10.1158/0008-5472.CAN-05-0141
90. Gubin MM, Zhang X, Schuster H, et al. Checkpoint blockade cancer immunotherapy targets tumour-specific mutant antigens. *Nature*. 2014;515 (7528):577–581. doi:10.1038/nature13988
91. Bengsch B, Johnson AL, Kurachi M, et al. Bioenergetic insufficiencies due to metabolic alterations regulated by the inhibitory receptor PD-1 are an early driver of CD8+ T cell exhaustion. *Immunity*. 2016;45(2):358–373. doi:10.1016/j.immuni.2016.07.008
92. Chang C-H, Qiu J, O'Sullivan D, et al. Metabolic competition in the tumor microenvironment is a driver of cancer progression. *Cell*. 2015;162 (6):1229–1241. doi:10.1016/j.cell.2015.08.016
93. Ho P-C, Bihuniak JD, Macintyre AN, et al. Phosphoenolpyruvate is a metabolic checkpoint of anti-tumor T cell responses. *Cell*. 2015;162 (6):1217–1228. doi:10.1016/j.cell.2015.08.012
94. Siska PJ, van der Windt GJ, Kishton RJ, et al. Suppression of Glut1 and glucose metabolism by decreased Akt/mTORC1 signaling drives T cell impairment in B cell leukemia. *J Immunol*. 2016;197(6):2532–2540. doi:10.4049/jimmunol.1502464
95. Frauwirth KA, Riley JL, Harris MH, et al. The CD28 signaling pathway regulates glucose metabolism. *Immunity*. 2002;16(6):769–777. doi:10.1016/S1074-7613(02)00323-0
96. Geltink RIK, O'Sullivan D, Corrado M, et al. Mitochondrial priming by CD28. *Cell*. 2017;171(2):385–97. e11. doi:10.1016/j.cell.2017.08.018
97. Hui E, Cheung J, Zhu J, et al. T cell costimulatory receptor CD28 is a primary target for PD-1–mediated inhibition. *Science*. 2017;355 (6332):1428–1433. doi:10.1126/science.aaf1292
98. Kamphorst AO, Wieland A, Nasti T, et al. Rescue of exhausted CD8 T cells by PD-1–targeted therapies is CD28-dependent. *Science*. 2017;355 (6332):1423–1427. doi:10.1126/science.aaf0683
99. Messmer AS, Que Y-A, Schankin C, et al. CAR T-cell therapy and critical care. *Wien Klin Wochenschr*. 2021:1–8. doi:10.1007/s00508-021-01948-2
100. Pilipow K, Darwich A, Losurdo A. T-cell-based breast cancer immunotherapy. *Semin Cancer Biol*. 2021;72:90–101. doi:10.1016/j.semcancer.2020.05.019
101. O'Neill LA, Kishton RJ, Rathmell J. A guide to immunometabolism for immunologists. *Nat Rev Immunol*. 2016;16(9):553–565. doi:10.1038/nri.2016.70
102. Chang C-H, Pearce EL. Emerging concepts of T cell metabolism as a target of immunotherapy. *Nat Immunol*. 2016;17(4):364–368. doi:10.1038/ni.3415
103. Freen-van Heeren JJ. Using CRISPR to enhance T cell effector function for therapeutic applications. *Cytokine: X*. 2021;3(1):100049. doi:10.1016/j.cytox.2020.100049
104. Riese MJ, Moon EK, Johnson BD, Albelda SM. Diacylglycerol kinases (DGKs): novel targets for improving T cell activity in cancer. *Front Cell Develop Biol*. 2016;4:108. doi:10.3389/fcell.2016.00108
105. Eichmann TO, Lass A. DAG tales: the multiple faces of diacylglycerol—stereochemistry, metabolism, and signaling. *Cell Mol Life Sci*. 2015;72 (20):3931–3952. doi:10.1007/s00018-015-1982-3
106. Jung I-Y, Kim -Y-Y, Yu H-S, Lee M, Kim S, Lee J. CRISPR/Cas9-mediated knockout of DGK improves antitumor activities of human T cells. *Cancer Res*. 2018;78(16):4692–4703. doi:10.1158/0008-5472.CAN-18-0030
107. Kawalekar OU, O'Connor RS, Fraietta JA, et al. Distinct signaling of coreceptors regulates specific metabolism pathways and impacts memory development in CAR T cells. *Immunity*. 2016;44(2):380–390. doi:10.1016/j.immuni.2016.01.021
108. Shim JS, Liu JO. Recent advances in drug repositioning for the discovery of new anticancer drugs. *Int J Biol Sci*. 2014;10(7):654. doi:10.7150/ijbs.9224
109. Gunton JE, Delhanty PJ, Takahashi S-I, Baxter RC. Metformin rapidly increases insulin receptor activation in human liver and signals preferentially through insulin-receptor substrate-2. *J Clin Endocrinol Metab*. 2003;88(3):1323–1332. doi:10.1210/jc.2002-021394
110. Kasznicki J, Sliwinska A, Drzewoski J. Metformin in cancer prevention and therapy. *Ann Transl Med*. 2014;2(6). doi:10.3978/j.issn.2305-5839.2014.06.01
111. Kishton RJ, Sukumar M, Restifo NP. Metabolic regulation of T cell longevity and function in tumor immunotherapy. *Cell Metab*. 2017;26 (1):94–109. doi:10.1016/j.cmet.2017.06.016
112. Morales DR, Morris AD. Metformin in cancer treatment and prevention. *Annu Rev Med*. 2015;66(1):17–29. doi:10.1146/annurev-med-062613-093128
113. Eikawa S, Nishida M, Mizukami S, Yamazaki C, Nakayama E, Udono H. Immune-mediated antitumor effect by type 2 diabetes drug, metformin. *Proc Nat Acad Sci*. 2015;112(6):1809–1814. doi:10.1073/pnas.1417636112
114. Araki K, Turner AP, Shaffer VO, et al. mTOR regulates memory CD8 T-cell differentiation. *Nature*. 2009;460(7251):108–112. doi:10.1038/nature08155
115. Wullschleger S, Loewith R, Hall MN. TOR signaling in growth and metabolism. *Cell*. 2006;124(3):471–484. doi:10.1016/j.cell.2006.01.016
116. Possemato R, Marks KM, Shaul YD, et al. Functional genomics reveal that the serine synthesis pathway is essential in breast cancer. *Nature*. 2011;476(7360):346–350. doi:10.1038/nature10350
117. Jaccard A, Wenes M, Gyülvészi G, Ho P-C, Romero P. 515 Metabolic reprogramming of antitumor CD8+ T cell immunity. *BMJ Specialist J*. 2020:8:1
118. Lochner M, Berod L, Sparwasser T. Fatty acid metabolism in the regulation of T cell function. *Trends Immunol*. 2015;36(2):81–91. doi:10.1016/j.it.2014.12.005
119. Kim D, Wu Y, Li Q, Oh Y-K. Nanoparticle-mediated lipid metabolic reprogramming of T cells in tumor microenvironments for immunometabolic therapy. *Nanomicro Lett*. 2021;13(1):1–27. doi:10.1007/s40820-020-00555-6
120. Leone RD, Zhao L, Englert JM, et al. Glutamine blockade induces divergent metabolic programs to overcome tumor immune evasion. *Science*. 2019;366(6468):1013–1021. doi:10.1126/science.aav2588
121. Renner K, Bruss C, Schnell A, et al. Restricting glycolysis preserves T cell effector functions and augments checkpoint therapy. *Cell Rep*. 2019;29(1):135–50. e9. doi:10.1016/j.celrep.2019.08.068