Immune Cell Type-Specific Metabolic Reprogramming

Subjects: Biochemistry & Molecular Biology | Endocrinology & Metabolism | Cell Biology
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Immunometabolism is an emerging discipline in cancer immunotherapy. Tumor tissues are heterogeneous and influenced by metabolic reprogramming of the tumor immune microenvironment (TIME). In the TIME, multiple cell types interact, and the tumor and immune cells compete for limited nutrients, resulting in altered anticancer immunity. Therefore, metabolic reprogramming of individual cell types may influence the outcomes of immunotherapy. Understanding the metabolic competition for access to limited nutrients between tumor cells and immune cells could reveal the breadth and complexity of the TIME and aid in developing novel therapeutic approaches for cancer.

Keywords: immunometabolism ; tumor microenvironment ; metabolic reprogramming ; immune checkpoint inhibitor

1. Introduction

Immunometabolism [1] is defined as the interplay between intracellular metabolic reprogramming and immunity. Cancer immunotherapy [2] is an advanced therapeutic modality; however, only some patients respond to expensive immunotherapeutic regimens. Tumor metabolism [3] has been widely studied and is a hallmark of cancer [4]. Cancer cells require sufficient nutrients [5] to appropriately adapt to the tumor immune microenvironment (TIME) and create a favorable metabolic environment for themselves. Most tumor tissues are heterogeneous and composed of various immune and stromal cells that communicate with each other, contributing to the reprogrammed metabolic environment. Although several studies have reported the influence of metabolic reprogramming [6] on immunotherapeutic responses, a more thorough understanding of the mechanistical implication of cell type-specific metabolic reprogramming in therapeutic responses is necessary to improve immune-directed cancer therapy. Immune cells that undergo metabolic reprogramming have extensive requirements for nutrients, such as glucose, glutamine, and fatty acids (FAs), which are metabolized to produce adenosine triphosphate (ATP) for energy expenditure [7].

Metabolically reprogrammed tumor cells in the TIME suppress immunity and render immune cells incapable of acquiring sufficient nutrients for optimal functioning. As metabolic reprogramming of different types of cells in the TIME can impact responses to immunotherapy [8], investigating the metabolic alterations or vulnerabilities of each cell type can have broad implications for next-level immune-directed anticancer therapy. Further, nutrients are not equally available to all immune cells, and metabolic reprogramming can alter the proportions of nutrients that are available to and consumed by cells. Therefore, by altering or inhibiting cellular metabolism in patients who do not respond to immunotherapy, the current anticancer immunotherapy approaches can be transformed to wide-ranging applications. Understanding the metabolic reprogramming of immune cells [8] at the single-cell level can also aid the development of potential therapeutic strategies to improve the effectiveness of anticancer immune responses by modulating immune cell functions.

2. Immune Cell Type-Specific Metabolic Reprogramming

2.1. T Cells

T cells are trained in the thymus and divided into the following four main types, based on their functions: killer (cytotoxic) T, T helper (Th), regulatory T (Tregs), and memory T cells. T cells use different metabolic pathways, depending on their subtype, and the effect of metabolic reprogramming increases, according to the differentiation degree and function of T cells [9]. An increased rate of glycolysis and abundance of proteins, lipids, and nucleotides are typical metabolic features of T cells [10]. Compared with naïve and memory T cells, cytotoxic T cells require more energy [11]. Accordingly, metabolic reprogramming plays a critical role in T cell fate and distinct function [12]. In particular, undifferentiated, naïve T cells mainly exploit FA oxidation (FAO) and oxidative phosphorylation (OXPHOS) for energy production [13], and glutamine metabolism [14] is needed to support cell growth and effector T (T eff) cell differentiation and function [15]. T eff cells utilize glycolysis [16], as well as leucine, serine, and tryptophan metabolism, among other mechanisms, for proper function and clonal proliferation [17][18]; memory T cells use FAO and OXPHOS, which are required for their sustained functional state [19]. Tregs mainly rely on OXPHOS [20], and their function and metabolic stability are maintained via the mTORC/c-MYC

signaling pathway [21]. Despite the distinct metabolic differences between T eff cells and Tregs, no significant differences in metabolic reprogramming have been revealed within T eff subpopulations [22].

For T cells to grow and differentiate in the TIME, progenitor cells need to function properly and must successfully compete against tumor cells for nutrients to acquire more energy and metabolic substrates. The checkpoint protein programmed death-1 (PD-1) affects T cell metabolism by inhibiting glycolysis, while promoting lipolysis and FAO [23], thus creating a potentially tolerogenic immune context. After T cell differentiation, metabolic reprogramming leads to their activation through a specific mechanism [24]. For example, amino acid and glucose transporters are upregulated via TCR-mediated signaling on the T cell surface [25]. Further, during the reliance of T cell differentiation on OXPHOS, metabolic reprogramming is essential for obtaining oxidizable energy substrates [13]. Glutamine metabolism is important for the proliferation and differentiation of Th1, Th17, and T eff $CD8^+$ T cells [26], whereas serine metabolism promotes the proliferation and survival of T cells through one-carbon metabolism [27].

At the metabolic level, various T cell subsets, such as T eff, Th1, Th2, and Th17 cells, as well as Tregs, express and secrete various cytokines; differential cytokine expression then alters the metabolic activity of specific cell types, eventually reshaping the immune environment [28]. Different glycolytic and lipid metabolic mechanisms are needed for T eff cells and $CD4^+$ T cells [29]. Thus, glycolysis inhibition during Th17 cell differentiation favors the formation of Tregs over Th17 cells [30], indicating a metabolic preference for T cell subset differentiation. Addition of exogenous FAs to cultures of activated T cells inhibits the production of Th1, Th2, and Th17 cytokines but does not affect Tregs [29]. Acetyl-CoA carboxylase 1 (ACC1) also promotes activation-induced metabolic reprogramming in T cells and Th1 and Th17 cell differentiation [31]. Inhibition of the PD-1/programmed death ligand-1 (PD-L1) pathway promotes transitory T eff cell recovery, unless the metabolic defect in exhausted tumor-specific T cells is fully remedied, in which case, the effects of the inherent metabolic reprogramming profile in an exhausted T cell subset are reduced [32]. Upon PD-1 ligation, activated T cells cannot utilize glycolysis or amino acid metabolism but show an increased rate of FAO, which is associated with a longer T cell lifespan [23].

T cells that have received the PD-1 signal show high levels of cysteine–glutathione (GSH) disulfide, ophthalmate, and GSH-like products, which are synthesized by the same enzymes, glutamylcysteine synthetase (GCS), and glutathione synthetase (GS). To further increase the rate of GSH synthesis, a more reductive environment is created in T cells in response to PD-1 signaling, along with a more pronounced decrease in the levels of reduced GSH [23]. In this case, modulation of hypoxia levels in the TIME may be an important metabolic target for T cell function [33], by directly affecting the redox balance in relation to GSH regeneration. Metformin is known to reduce hypoxia levels in the TIME by decreasing oxygen consumption of tumor cells. Metformin also improves the response to PD-1 blockade in tumor models that are resistant to checkpoint blockade [34]. In addition to PD-1, the lymphocyte activation gene 3 (*LAG3*) is an inhibitory molecule expressed on T cells. Targeting *LAG3* may be a novel approach in antitumor therapy by the regulation of T cell metabolism by preventing excessive proliferation of naïve T cells and inhibiting IL-7-mediated STAT5 activation, while increasing mitochondria takes advantage of the increased oxidation and glycolytic metabolism [35]. In terms of targeting T cell lipid metabolism, fenofibrate activates PPARα to increase FAO by T cells, thus reversing the inhibitory the effect of T cells in the microenvironment [36]. In terms of targeting T cell amino acid metabolism, when PD-1 expression is decreased in $CD8^+$ T cells under glutamine-limited conditions, KI67 and prosurvival protein expression is increased, suggesting a promising approach for adaptive immunotherapy [37].

Thus, changing the metabolic profiles can enhance the antitumor effector functions of T cells [38]. Future studies are required to elucidate how PD-1 induces metabolic alterations and immunosuppressive responses via mutual signaling crosstalk between T cells, cancer cells, and other cell types.

2.2. B Cells

B cells play roles in adaptive immunity, such as antigen presentation and cytokine secretion, but are most commonly known as producers of tumor-reactive antibodies (Abs) [39]. B cells are abundant in tumors and have two opposite effects from an immunity viewpoint. First, B cells promote tumor cell inhibition via NK cells and macrophages; second, regulatory B cells [40] directly or indirectly inhibit Th1 cell and $CD8^+$ cytolytic T cell responses, thereby contributing to tumor development. B cells mainly utilize glucose and are metabolically activated to obtain energy for activating their antigen receptors. Adipogenesis is required during the differentiation of plasma cells and responsible for the production of large amounts of high-affinity Abs [41]. Under hypoxic conditions, B cells use glutamine through the glucose-independent TCA cycle to proliferate and survive [42]. IL-4 signaling triggers BCL6 expression and germinal center B cell differentiation and alters the TCA cycle to produce α-ketoglutarate, a cofactor for H3K27 demethylase [43]. B cell-specific loss of GLUT1 decreases B cell numbers and impairs Ab production, and activated B cells demand GLUT1-dependent metabolic

reprogramming for their proliferation and Ab production [44]. B cells also affect immunotherapy responses by releasing Abs and activating T cells [45].

Because PD-1, PD-L1, CTLA-4, and B7 are expressed on the B cell surface, therapeutic ICB can target activated B cells. In addition, both CTLA-4 and PD-1 inhibit B cell activity, and blocking either molecule increases the production and proliferation of memory B cells [46][47].

2.3. Macrophages

Macrophages are immune cells that feed on enemies, such as pathogens, that invade the human body or secrete toxins to destroy and eliminate pathogens. The mechanism by which M1 macrophages are transformed to M2 macrophages is called macrophage polarization [48]. M1 polarization has been linked with antineoplastic activity [49]. Distinct metabolic features of the TIME promote tumor growth [50], and the metabolic differences between M1 and M2 macrophages in the TIME have different effects on anticancer immunity [51]. While M1 macrophages mainly use glycolysis and the pentose phosphate pathway (PPP) [52], but not the TCA cycle [53], M2 macrophages use OXPHOS and FAO [54]. M2 macrophages are sustained by the TCA cycle and fuel OXPHOS with glutamine and FAs [55].

Metabolic reprogramming in macrophages is rather complex [56]. Although the glycolytic signature does not appear in fully activated M2 macrophages, it plays an important role in M2 activation. Lactic acid is a key player in inducing M2-like polarization of tumor-associated macrophages (TAMs) [57], which activate tumor growth via reprogrammed immunomodulation. Correctly functioning M2 macrophages increase immunosuppression and tumor development through immunosuppressive cytokines, thereby leading to immunotherapy resistance [58].

M1 macrophages exhibit proinflammatory properties and support metabolic flux through increased levels of glycolysis, the PPP, and FA synthesis, along with decreased rates of OXPHOS and the TCA cycle; however, M2 macrophages exhibit increased OXPHOS rates and activated FAO [59][60]. Changes in the metabolic landscape promote tumor development, and M2 macrophages have been shown to enhance IL-1β secretion, as well as increase metastasis, proliferation, and invasion of hepatocellular carcinoma cells, via the FAO pathway [61]. Moreover, increased levels of glycolysis in macrophages are associated with PD-L1 expression through the upregulation of the TAM glycolytic enzyme, PFKFB3 [62].

Under hypoxic conditions, the transcription factor HIF plays a critical role as a mediator of metabolic reprogramming in macrophages [63]. Under these conditions, M1 macrophages rely on glycolysis, which depends on HIF1α activity [64]. HIF1α, whose expression is regulated by transcription factors, such as NF-κB, which, in turn, induces the production of proinflammatory cytokines and glycolytic enzymes in M1 macrophages; in contrast, HIF2α expression is independent of NF-κB, and does not trigger these changes [64]. Therefore, highly glycolytic tumor cells and M1 macrophages are speculated to compete for glucose in the TIME. Thus, in theory, inhibiting tumor cell-specific glycolysis should enhance the anticancer effect of M1 macrophages.

Alternatively, GB111-NH2, a cysteine cathepsin inhibitor, is related to lipid metabolism and induces a polarization change from M2 to M1 macrophages [65]. The use of GB111-NH2 as a pharmacological agent could, therefore, be a beneficial immunotherapeutic approach. Taken together, anticancer immunotherapy that targets macrophage metabolic reprogramming has tremendous potential and urgently needs further research.

2.4. NK Cells

NK cells have become a valuable tool in cancer immunotherapy because they can potentially kill tumor cells [66]. NK cells preferentially depend on glycolysis and glucose metabolism by OXPHOS for ATP production, which promotes their effector function and rapid proliferation [67]. Low arginine concentrations impair NK cell proliferation and IFNγ production [68]. mTORC1 is necessary for the increased glycolysis induction [69], and mTOR signaling is reported to be inhibited in a leucine-depleted medium [70]. Taken together, this information indicates that NK cells are sensitive to the metabolic profile of the TIME, which influences NK cell-mediated anticancer immunity.

Increased OXPHOS rates are required for the functional responses of NK cells; however, the mechanisms involved in the induction of mitochondrial metabolism in cytokine-activated NK cells have not been reported [71]. NK cells upregulate HIF1α expression in response to hypoxia but cannot increase the expression levels of key activated surface receptors in response to cytokines [72]. However, the metabolic responses of NK cells have been linked with cMYC expression [70]. Glutamine-regulated cMYC expression plays an important but variable metabolic role in regulating NK cell growth and responses [70]. Although some amino acids serve as metabolic regulators, without being used as fuel, amino acids may be required for NK cell function; stimulation of NK cells with IL-2, IL-15, or IL-18 increases the levels of amino acid

transporters [73]. In this regard, mTORC1 activation has been shown to control NK cell antitumor responses [74]. Combinations of immune checkpoint inhibitors such as CTLA-4 and PD-1, which can target T cells, are also implicated in NK cell-mediated cytotoxicity [75]. On the contrary, NK cells may be resilient in their use of the metabolic energy sources related to immune function, as glutamine starvation does not decrease IFNγ production [76]. Thus, it is necessary to understand the metabolic flexibility of NK cells and how they resist the metabolically restrictive TIME by studying their metabolic properties and interactions with other immune cells [66].

A novel immune checkpoint-blocking strategy has been reported with the potential to reverse NK cell dysfunction in cancer, based on the ability of anti-PD-1 or anti-PD-L1 Abs to enhance the antitumor efficacy of NK cells [75]. NK cells depend mainly on OXPHOS for energy in the resting state, whereas glycolysis increases after activation [77]. FAs and cholesterol/oxysterols that induce PPAR activation and SREBP inhibition, fuel the OXPHOS in NK cells, and keep them in the resting state. Likewise, glucose and amino acid deficiencies inhibit the activity of nutrient sensors, including cMYC and mTOCR1, which are also important in NK cell immune functions. These alterations in the signaling pathway adversely affect NK cell metabolism, including glycolysis and OXPHOS, thereby impairing the antitumor responses of NK cells [77]. Therefore, targeting the metabolic reprogramming processes in NK cells is necessary to strengthen their immunostimulatory functions for improved immunotherapies.

2.5. Dendritic Cells

Dendritic cells (DCs) monitor tissues and can control innate and adaptive immunity as antigen-presenting cells capable of provoking naïve T cells via danger signals, derived from microorganisms and tissues [78]. DCs contain glycogen stores and are important for facilitating an immediate glycolytic response upon lipopolysaccharide (LPS) stimulation [79]. Glycolytic restriction during DC activation can either inhibit or enhance DC functions. Inhibition of glycolysis during the initial activation step impairs DC function, whereas 8 h after activation, glycolysis induces the proinflammatory function of DCs and T cell responses [80][81]. Glycolysis rates rapidly increase, following Toll-like receptor (TLR) stimulation, to maintain DC activation and lifespan [82]. Lipid metabolism is also important for DCs. C75 (FA synthase inhibitor) or TOFA (ACC1 inhibitor) can inhibit DC activation upon LPS stimulation, leading to the dysfunction and inactivation of antigen-restricted CD4 T cells or NK cells [83].

Ligation of TLR results in DC activation. When TLR agonists activate DCs, they undergo metabolic reprogramming, including a shift away from mitochondrial lipid oxidation and OXPHOS, toward enhanced aerobic glycolysis [51]. The increased glycolytic flux plays an essential role in the de novo fatty acid synthesis for expanding the endoplasmic reticulum and Golgi apparatus, which are required for the production and secretion of proteins and cytokines to drive proper immune responses [84]. Therefore, DC activation, maturation, and immunogenic activities are all aided by glycolysis. Tolerogenic DCs, similar to M2 macrophages, have a metabolic profile that differs from immunogenic DCs, with increased mitochondrial metabolism and OXPHOS [85]. Tolerogenic DCs have immature and inactivated characteristics, which favor Treg induction and immunological suppression, whereas tumor-derived DCs, with tolerogenic activities, have decreased glycolysis but increased lipid storage, resulting in impaired APC functions and T cell priming [86]. Thus, TLR agonist-mediated metabolic reprogramming of DCs in the TIME can be a potential novel strategy to enhance anti-cancer immunity in cancer immunotherapy.

2.6. Myeloid-Derived Suppressor Cells

With respect to cancer immunity, myeloid-derived suppressor cells (MDSCs) inhibit the activities of T cells and NK cells [87] to promote tumor growth and play a role in premetastatic niche development; MDSCs also have a mechanism that contributes to their resistance to immunotherapy [88]. MDSCs undergo metabolic reprogramming in tumors and exhibit immunosuppression by increasing the β-oxidation of FAs [89]. Granulocytic MDSCs primarily depend on glycolysis and very low levels of OXPHOS [90], whereas inflammatory neutrophilic MDSCs contain glycogen deposits, which can serve as intracellular fuel stores to sustain glycolysis in the absence of glucose [91]. Depletion of essential amino acids via amino acid metabolism and generation of oxidative stress play important roles in the inhibitory activity of MDSCs against T cells [87]. For instance, MDSCs can deplete L-arginine via metabolism by ARG1 and cause L-cysteine deficiency. Depletion of this amino acid leads to the downregulation of the TCR z-chain and suppresses T cell proliferation [92]. Expression of NOS2, ARG1, and NADPH oxidase, by MDSCs, results in the generation of reactive nitrogen and reactive oxygen species (ROS). These reactive molecules downregulate the TCR z-chain and IL-2 receptor signaling, which are required to induce T cell activation and proliferation, whereas granulocytic MDSCs use ROS for immunosuppression [87].

References

1. O'Neill, L.A.; Kishton, R.J.; Rathmell, J. A guide to immunometabolism for immunologists. Nat. Rev. Immunol. 2016, 16, 553–565.
2. Waldman, A.D.; Fritz, J.M.; Lenardo, M.J. A guide to cancer immunotherapy: From T cell basic science to clinical practice. Nat. Rev. Immunol. 2020, 20, 651–668.
3. Martinez-Reyes, I.; Chandel, N.S. Cancer metabolism: Looking forward. Nat. Rev. Cancer 2021, 21, 669–680.
4. Hanahan, D.; Weinberg, R.A. Hallmarks of cancer: The next generation. Cell 2011, 144, 646–674.
5. Frades, I.; Foguet, C.; Cascante, M.; Arauzo-Bravo, M.J. Genome Scale Modeling to Study the Metabolic Competition between Cells in the Tumor Microenvironment. Cancers 2021, 13, 4609.
6. Xiao, Z.; Dai, Z.; Locasale, J.W. Metabolic landscape of the tumor microenvironment at single cell resolution. Nat. Commun. 2019, 10, 3763.
7. Kedia-Mehta, N.; Finlay, D.K. Competition for nutrients and its role in controlling immune responses. Nat. Commun. 2019, 10, 2123.
8. Cerezo, M.; Rocchi, S. Cancer cell metabolic reprogramming: A keystone for the response to immunotherapy. Cell Death Dis. 2020, 11, 964.
9. Ricciardi, S.; Manfrini, N.; Alfieri, R.; Calamita, P.; Crosti, M.C.; Gallo, S.; Muller, R.; Pagani, M.; Abrignani, S.; Biffo, S. The Translational Machinery of Human CD4+ T Cells Is Poised for Activation and Controls the Switch from Quiescence to Metabolic Remodeling. Cell Metab. 2018, 28, 895–906.e895.
10. Pearce, E.L.; Poffenberger, M.C.; Chang, C.H.; Jones, R.G. Fueling immunity: Insights into metabolism and lymphocyte function. Science 2013, 342, 1242454.
11. Konjar, S.; Veldhoen, M. Dynamic Metabolic State of Tissue Resident CD8 T Cells. Front. Immunol. 2019, 10, 1683.
12. Patsoukis, N.; Bardhan, K.; Weaver, J.; Herbel, C.; Seth, P.; Li, L.; Boussiotis, V.A. The role of metabolic reprogramming in T cell fate and function. Curr. Trends Immunol. 2016, 17, 1–12.
13. Buck, M.D.; O'Sullivan, D.; Pearce, E.L. T cell metabolism drives immunity. J. Exp. Med. 2015, 212, 1345–1360.
14. Sears, J.D.; Waldron, K.J.; Wei, J.; Chang, C.H. Targeting metabolism to reverse T-cell exhaustion in chronic viral infections. Immunology 2021, 162, 135–144.
15. Rathmell, J.C.; Vander Heiden, M.G.; Harris, M.H.; Frauwirth, K.A.; Thompson, C.B. In the absence of extrinsic signals, nutrient utilization by lymphocytes is insufficient to maintain either cell size or viability. Mol. Cell 2000, 6, 683–692.
16. Saka, D.; Gokalp, M.; Piyade, B.; Cevik, N.C.; Arik Sever, E.; Unutmaz, D.; Ceyhan, G.O.; Demir, I.E.; Asimgil, H. Mechanisms of T-Cell Exhaustion in Pancreatic Cancer. Cancers 2020, 12, 2274.
17. Sinclair, L.V.; Rolf, J.; Emslie, E.; Shi, Y.B.; Taylor, P.M.; Cantrell, D.A. Control of amino-acid transport by antigen receptors coordinates the metabolic reprogramming essential for T cell differentiation. Nat. Immunol. 2013, 14, 500–508.
18. Ma, E.H.; Bantug, G.; Griss, T.; Condotta, S.; Johnson, R.M.; Samborska, B.; Mainolfi, N.; Suri, V.; Guak, H.; Balmer, M.L.; et al. Serine Is an Essential Metabolite for Effector T Cell Expansion. Cell Metab. 2017, 25, 345–357.
19. Assmann, J.C.; Farthing, D.E.; Saito, K.; Maglakelidze, N.; Oliver, B.; Warrick, K.A.; Sourbier, C.; Ricketts, C.J.; Meyer, T.J.; Pavletic, S.Z.; et al. Glycolytic metabolism of pathogenic T cells enables early detection of GVHD by 13C-MRI. Blood 2021, 137, 126–137.
20. Buszko, M.; Shevach, E.M. Control of regulatory T cell homeostasis. Curr. Opin. Immunol. 2020, 67, 18–26.
21. Wei, J.; Long, L.; Yang, K.; Guy, C.; Shrestha, S.; Chen, Z.; Wu, C.; Vogel, P.; Neale, G.; Green, D.R.; et al. Autophagy enforces functional integrity of regulatory T cells by coupling environmental cues and metabolic homeostasis. Nat. Immunol. 2016, 17, 277–285.
22. Barnes, M.J.; Powrie, F. Regulatory T cells reinforce intestinal homeostasis. Immunity 2009, 31, 401–411.
23. Patsoukis, N.; Bardhan, K.; Chatterjee, P.; Sari, D.; Liu, B.; Bell, L.N.; Karoly, E.D.; Freeman, G.J.; Petkova, V.; Seth, P.; et al. PD-1 alters T-cell metabolic reprogramming by inhibiting glycolysis and promoting lipolysis and fatty acid oxidation. Nat. Commun. 2015, 6, 6692.
24. Parry, R.V.; Chemnitz, J.M.; Frauwirth, K.A.; Lanfranco, A.R.; Braunstein, I.; Kobayashi, S.V.; Linsley, P.S.; Thompson, C.B.; Riley, J.L. CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. Mol. Cell. Biol. 2005, 25, 9543–9553.

25. Ren, W.; Liu, G.; Yin, J.; Tan, B.; Wu, G.; Bazer, F.W.; Peng, Y.; Yin, Y. Amino-acid transporters in T-cell activation and differentiation. Cell Death Dis. 2017, 8, e2757.

26. Johnson, M.O.; Wolf, M.M.; Madden, M.Z.; Andrejeva, G.; Sugiura, A.; Contreras, D.C.; Maseda, D.; Liberti, M.V.; Paz, K.; Kishton, R.J.; et al. Distinct Regulation of Th17 and Th1 Cell Differentiation by Glutaminase-Dependent Metabolism. Cell 2018, 175, 1780–1795.e1719.

27. Ron-Harel, N.; Santos, D.; Ghergurovich, J.M.; Sage, P.T.; Reddy, A.; Lovitch, S.B.; Dephoure, N.; Satterstrom, F.K.; Sheffer, M.; Spinelli, J.B.; et al. Mitochondrial Biogenesis and Proteome Remodeling Promote One-Carbon Metabolism for T Cell Activation. Cell Metab. 2016, 24, 104–117.

28. Sakaguchi, S.; Yamaguchi, T.; Nomura, T.; Ono, M. Regulatory T cells and immune tolerance. Cell 2008, 133, 775–787.

29. Michalek, R.D.; Gerriets, V.A.; Jacobs, S.R.; Macintyre, A.N.; MacIver, N.J.; Mason, E.F.; Sullivan, S.A.; Nichols, A.G.; Rathmell, J.C. Cutting edge: Distinct glycolytic and lipid oxidative metabolic programs are essential for effector and regulatory CD4+ T cell subsets. J. Immunol. 2011, 186, 3299–3303.

30. Shi, L.Z.; Wang, R.; Huang, G.; Vogel, P.; Neale, G.; Green, D.R.; Chi, H. HIF1alpha-dependent glycolytic pathway orchestrates a metabolic checkpoint for the differentiation of TH17 and Treg cells. J. Exp. Med. 2011, 208, 1367–1376.

31. Berod, L.; Friedrich, C.; Nandan, A.; Freitag, J.; Hagemann, S.; Harmrolfs, K.; Sandouk, A.; Hesse, C.; Castro, C.N.; Bahre, H.; et al. De novo fatty acid synthesis controls the fate between regulatory T and T helper 17 cells. Nat. Med. 2014, 20, 1327–1333.

32. Herbel, C.; Patsoukis, N.; Bardhan, K.; Seth, P.; Weaver, J.D.; Boussiotis, V.A. Clinical significance of T cell metabolic reprogramming in cancer. Clin. Transl. Med. 2016, 5, 29.

33. Rivadeneira, D.B.; Delgoffe, G.M. Antitumor T-cell Reconditioning: Improving Metabolic Fitness for Optimal Cancer Immunotherapy. Clin. Cancer Res. 2018, 24, 2473–2481.

34. Scharping, N.E.; Menk, A.V.; Whetstone, R.D.; Zeng, X.; Delgoffe, G.M. Efficacy of PD-1 Blockade Is Potentiated by Metformin-Induced Reduction of Tumor Hypoxia. Cancer Immunol. Res. 2017, 5, 9–16.

35. Previte, D.M.; Martins, C.P.; O'Connor, E.C.; Marre, M.L.; Coudriet, G.M.; Beck, N.W.; Menk, A.V.; Wright, R.H.; Tse, H.M.; Delgoffe, G.M.; et al. Lymphocyte Activation Gene-3 Maintains Mitochondrial and Metabolic Quiescence in Naive CD4+ T Cells. Cell Rep. 2019, 27, 129–141.e124.

36. Zhang, Y.; Kurupati, R.; Liu, L.; Zhou, X.Y.; Zhang, G.; Hudaihed, A.; Filisio, F.; Giles-Davis, W.; Xu, X.; Karakousis, G.C.; et al. Enhancing CD8+ T Cell Fatty Acid Catabolism within a Metabolically Challenging Tumor Microenvironment Increases the Efficacy of Melanoma Immunotherapy. Cancer Cell 2017, 32, 377–391.e379.

37. Nabe, S.; Yamada, T.; Suzuki, J.; Toriyama, K.; Yasuoka, T.; Kuwahara, M.; Shiraishi, A.; Takenaka, K.; Yasukawa, M.; Yamashita, M. Reinforce the antitumor activity of CD8+ T cells via glutamine restriction. Cancer Sci. 2018, 109, 3737–3750.

38. Ho, P.C.; Bihuniak, J.D.; Macintyre, A.N.; Staron, M.; Liu, X.; Amezquita, R.; Tsui, Y.C.; Cui, G.; Micevic, G.; Perales, J.C.; et al. Phosphoenolpyruvate Is a Metabolic Checkpoint of Anti-tumor T Cell Responses. Cell 2015, 162, 1217–1228.

39. Yuen, G.J.; Demissie, E.; Pillai, S. B lymphocytes and cancer: A love-hate relationship. Trends Cancer 2016, 2, 747–757.

40. Balkwill, F.; Montfort, A.; Capasso, M. B regulatory cells in cancer. Trends Immunol. 2013, 34, 169–173.

41. Dufort, F.J.; Gumina, M.R.; Ta, N.L.; Tao, Y.; Heyse, S.A.; Scott, D.A.; Richardson, A.D.; Seyfried, T.N.; Chiles, T.C. Glucose-dependent de novo lipogenesis in B lymphocytes: A requirement for atp-citrate lyase in lipopolysaccharide-induced differentiation. J. Biol. Chem. 2014, 289, 7011–7024.

42. Le, A.; Lane, A.N.; Hamaker, M.; Bose, S.; Gouw, A.; Barbi, J.; Tsukamoto, T.; Rojas, C.J.; Slusher, B.S.; Zhang, H.; et al. Glucose-independent glutamine metabolism via TCA cycling for proliferation and survival in B cells. Cell Metab. 2012, 15, 110–121.

43. Haniuda, K.; Fukao, S.; Kitamura, D. Metabolic Reprogramming Induces Germinal Center B Cell Differentiation through Bcl6 Locus Remodeling. Cell Rep. 2020, 33, 108333.

44. Caro-Maldonado, A.; Wang, R.; Nichols, A.G.; Kuraoka, M.; Milasta, S.; Sun, L.D.; Gavin, A.L.; Abel, E.D.; Kelsoe, G.; Green, D.R.; et al. Metabolic reprogramming is required for antibody production that is suppressed in anergic but exaggerated in chronically BAFF-exposed B cells. J. Immunol. 2014, 192, 3626–3636.

45. Hollern, D.P.; Xu, N.; Thennavan, A.; Glodowski, C.; Garcia-Recio, S.; Mott, K.R.; He, X.; Garay, J.P.; Carey-Ewend, K.; Marron, D.; et al. B Cells and T Follicular Helper Cells Mediate Response to Checkpoint Inhibitors in High Mutation Burden Mouse Models of Breast Cancer. Cell 2019, 179, 1191–1206.e1121.

46. Fanoni, D.; Tavecchio, S.; Recalcati, S.; Balice, Y.; Venegoni, L.; Fiorani, R.; Crosti, C.; Berti, E. New monoclonal antibodies against B-cell antigens: Possible new strategies for diagnosis of primary cutaneous B-cell lymphomas. Immunol. Lett. 2011, 134, 157–160.

47. Pardoll, D.M. The blockade of immune checkpoints in cancer immunotherapy. Nat. Rev. Cancer 2012, 12, 252–264.

48. Lawrence, T.; Natoli, G. Transcriptional regulation of macrophage polarization: Enabling diversity with identity. Nat. Rev. Immunol. 2011, 11, 750–761.

49. Duan, Z.; Luo, Y. Targeting macrophages in cancer immunotherapy. Signal Transduct. Target. Ther. 2021, 6, 127.

50. Mehla, K.; Singh, P.K. Metabolic Regulation of Macrophage Polarization in Cancer. Trends Cancer 2019, 5, 822–834.

51. Kelly, B.; O'Neill, L.A. Metabolic reprogramming in macrophages and dendritic cells in innate immunity. Cell Res. 2015, 25, 771–784.

52. Dai, X.; Lu, L.; Deng, S.; Meng, J.; Wan, C.; Huang, J.; Sun, Y.; Hu, Y.; Wu, B.; Wu, G.; et al. USP7 targeting modulates anti-tumor immune response by reprogramming Tumor-associated Macrophages in Lung Cancer. Theranostics 2020, 10, 9332–9347.

53. O'Neill, L.A.; Pearce, E.J. Immunometabolism governs dendritic cell and macrophage function. J. Exp. Med. 2016, 213, 15–23.

54. Yu, Y.; Cai, W.; Zhou, J.; Lu, H.; Wang, Y.; Song, Y.; He, R.; Pei, F.; Wang, X.; Zhang, R.; et al. Anti-arthritis effect of berberine associated with regulating energy metabolism of macrophages through AMPK/HIF-1alpha pathway. Int. Immunopharmacol. 2020, 87, 106830.

55. Murray, P.J.; Rathmell, J.; Pearce, E. SnapShot: Immunometabolism. Cell Metab. 2015, 22, 190–190.e1.

56. Liu, Y.; Xu, R.; Gu, H.; Zhang, E.; Qu, J.; Cao, W.; Huang, X.; Yan, H.; He, J.; Cai, Z. Metabolic reprogramming in macrophage responses. Biomark. Res. 2021, 9, 1.

57. Colegio, O.R.; Chu, N.Q.; Szabo, A.L.; Chu, T.; Rhebergen, A.M.; Jairam, V.; Cyrus, N.; Brokowski, C.E.; Eisenbarth, S.C.; Phillips, G.M.; et al. Functional polarization of tumour-associated macrophages by tumour-derived lactic acid. Nature 2014, 513, 559–563.

58. Mantovani, A.; Sica, A.; Sozzani, S.; Allavena, P.; Vecchi, A.; Locati, M. The chemokine system in diverse forms of macrophage activation and polarization. Trends Immunol. 2004, 25, 677–686.

59. Xia, Y.; Brown, Z.J.; Huang, H.; Tsung, A. Metabolic reprogramming of immune cells: Shaping the tumor microenvironment in hepatocellular carcinoma. Cancer Med. 2021, 10, 6374–6383.

60. Mills, E.L.; O'Neill, L.A. Reprogramming mitochondrial metabolism in macrophages as an anti-inflammatory signal. Eur. J. Immunol. 2016, 46, 13–21.

61. Zhang, Q.; Wang, H.; Mao, C.; Sun, M.; Dominah, G.; Chen, L.; Zhuang, Z. Fatty acid oxidation contributes to IL-1beta secretion in M2 macrophages and promotes macrophage-mediated tumor cell migration. Mol. Immunol. 2018, 94, 27–35.

62. Chen, D.P.; Ning, W.R.; Jiang, Z.Z.; Peng, Z.P.; Zhu, L.Y.; Zhuang, S.M.; Kuang, D.M.; Zheng, L.; Wu, Y. Glycolytic activation of peritumoral monocytes fosters immune privilege via the PFKFB3-PD-L1 axis in human hepatocellular carcinoma. J. Hepatol. 2019, 71, 333–343.

63. Talks, K.L.; Turley, H.; Gatter, K.C.; Maxwell, P.H.; Pugh, C.W.; Ratcliffe, P.J.; Harris, A.L. The expression and distribution of the hypoxia-inducible factors HIF-1alpha and HIF-2alpha in normal human tissues, cancers, and tumor-associated macrophages. Am. J. Pathol. 2000, 157, 411–421.

64. Galvan-Pena, S.; O'Neill, L.A. Metabolic reprograming in macrophage polarization. Front. Immunol. 2014, 5, 420.

65. Oelschlaegel, D.; Weiss Sadan, T.; Salpeter, S.; Krug, S.; Blum, G.; Schmitz, W.; Schulze, A.; Michl, P. Cathepsin Inhibition Modulates Metabolism and Polarization of Tumor-Associated Macrophages. Cancers 2020, 12, 2579.

66. Terren, I.; Orrantia, A.; Vitalle, J.; Zenarruzabeitia, O.; Borrego, F. NK Cell Metabolism and Tumor Microenvironment. Front. Immunol. 2019, 10, 2278.

67. Cong, J. Metabolism of Natural Killer Cells and Other Innate Lymphoid Cells. Front. Immunol. 2020, 11, 1989.

68. Lamas, B.; Vergnaud-Gauduchon, J.; Goncalves-Mendes, N.; Perche, O.; Rossary, A.; Vasson, M.P.; Farges, M.C. Altered functions of natural killer cells in response to L-Arginine availability. Cell Immunol. 2012, 280, 182–190.

69. Keating, S.E.; Zaiatz-Bittencourt, V.; Loftus, R.M.; Keane, C.; Brennan, K.; Finlay, D.K.; Gardiner, C.M. Metabolic Reprogramming Supports IFN-gamma Production by CD56bright NK Cells. J. Immunol. 2016, 196, 2552–2560.

70. Loftus, R.M.; Assmann, N.; Kedia-Mehta, N.; O'Brien, K.L.; Garcia, A.; Gillespie, C.; Hukelmann, J.L.; Oefner, P.J.; Lamond, A.I.; Gardiner, C.M.; et al. Amino acid-dependent cMyc expression is essential for NK cell metabolic and

functional responses in mice. Nat. Commun. 2018, 9, 2341.

71. Miranda, D.; Jara, C.; Ibanez, J.; Ahumada, V.; Acuna-Castillo, C.; Martin, A.; Cordova, A.; Montoya, M. PGC-1alpha-Dependent Mitochondrial Adaptation Is Necessary to Sustain IL-2-Induced Activities in Human NK Cells. Mediat. Inflamm. 2016, 2016, 9605253.
72. Balsamo, M.; Manzini, C.; Pietra, G.; Raggi, F.; Blengio, F.; Mingari, M.C.; Varesio, L.; Moretta, L.; Bosco, M.C.; Vitale, M. Hypoxia downregulates the expression of activating receptors involved in NK-cell-mediated target cell killing without affecting ADCC. Eur. J. Immunol. 2013, 43, 2756–2764.
73. Jensen, H.; Potempa, M.; Gotthardt, D.; Lanier, L.L. Cutting Edge: IL-2-Induced Expression of the Amino Acid Transporters SLC1A5 and CD98 Is a Prerequisite for NKG2D-Mediated Activation of Human NK Cells. J. Immunol. 2017, 199, 1967–1972.
74. Michelet, X.; Dyck, L.; Hogan, A.; Loftus, R.M.; Duquette, D.; Wei, K.; Beyaz, S.; Tavakkoli, A.; Foley, C.; Donnelly, R.; et al. Metabolic reprogramming of natural killer cells in obesity limits antitumor responses. Nat. Immunol. 2018, 19, 1330–1340.
75. Hsu, J.; Hodgins, J.J.; Marathe, M.; Nicolai, C.J.; Bourgeois-Daigneault, M.C.; Trevino, T.N.; Azimi, C.S.; Scheer, A.K.; Randolph, H.E.; Thompson, T.W.; et al. Contribution of NK cells to immunotherapy mediated by PD-1/PD-L1 blockade. J. Clin. Investig. 2018, 128, 4654–4668.
76. Presnell, S.R.; Spear, H.K.; Durham, J.; Riddle, T.; Applegate, A.; Lutz, C.T. Differential Fuel Requirements of Human NK Cells and Human CD8 T Cells: Glutamine Regulates Glucose Uptake in Strongly Activated CD8 T Cells. Immunohorizons 2020, 4, 231–244.
77. Wang, Z.; Guan, D.; Wang, S.; Chai, L.Y.A.; Xu, S.; Lam, K.P. Glycolysis and Oxidative Phosphorylation Play Critical Roles in Natural Killer Cell Receptor-Mediated Natural Killer Cell Functions. Front. Immunol. 2020, 11, 202.
78. Patente, T.A.; Pinho, M.P.; Oliveira, A.A.; Evangelista, G.C.M.; Bergami-Santos, P.C.; Barbuto, J.A.M. Human Dendritic Cells: Their Heterogeneity and Clinical Application Potential in Cancer Immunotherapy. Front. Immunol. 2018, 9, 3176.
79. Thwe, P.M.; Pelgrom, L.R.; Cooper, R.; Beauchamp, S.; Reisz, J.A.; D'Alessandro, A.; Everts, B.; Amiel, E. Cell-Intrinsic Glycogen Metabolism Supports Early Glycolytic Reprogramming Required for Dendritic Cell Immune Responses. Cell Metab. 2019, 30, 225.
80. Everts, B.; Amiel, E.; Huang, S.C.; Smith, A.M.; Chang, C.H.; Lam, W.Y.; Redmann, V.; Freitas, T.C.; Blagih, J.; van der Windt, G.J.; et al. TLR-driven early glycolytic reprogramming via the kinases TBK1-IKKvarepsilon supports the anabolic demands of dendritic cell activation. Nat. Immunol. 2014, 15, 323–332.
81. Lawless, S.J.; Kedia-Mehta, N.; Walls, J.F.; McGarrigle, R.; Convery, O.; Sinclair, L.V.; Navarro, M.N.; Murray, J.; Finlay, D.K. Glucose represses dendritic cell-induced T cell responses. Nat. Commun. 2017, 8, 15620.
82. Krawczyk, C.M.; Holowka, T.; Sun, J.; Blagih, J.; Amiel, E.; DeBerardinis, R.J.; Cross, J.R.; Jung, E.; Thompson, C.B.; Jones, R.G.; et al. Toll-like receptor-induced changes in glycolytic metabolism regulate dendritic cell activation. Blood 2010, 115, 4742–4749.
83. Ibrahim, J.; Nguyen, A.H.; Rehman, A.; Ochi, A.; Jamal, M.; Graffeo, C.S.; Henning, J.R.; Zambirinis, C.P.; Fallon, N.C.; Barilla, R.; et al. Dendritic cell populations with different concentrations of lipid regulate tolerance and immunity in mouse and human liver. Gastroenterology 2012, 143, 1061–1072.
84. Pearce, E.J.; Everts, B. Dendritic cell metabolism. Nat. Rev. Immunol. 2015, 15, 18–29.
85. Ferreira, G.B.; Kleijwegt, F.S.; Waelkens, E.; Lage, K.; Nikolic, T.; Hansen, D.A.; Workman, C.T.; Roep, B.O.; Overbergh, L.; Mathieu, C. Differential protein pathways in 1,25-dihydroxyvitamin d(3) and dexamethasone modulated tolerogenic human dendritic cells. J. Proteome Res. 2012, 11, 941–971.
86. Herber, D.L.; Cao, W.; Nefedova, Y.; Novitskiy, S.V.; Nagaraj, S.; Tyurin, V.A.; Corzo, A.; Cho, H.I.; Celis, E.; Lennox, B.; et al. Lipid accumulation and dendritic cell dysfunction in cancer. Nat. Med. 2010, 16, 880–886.
87. Gabrilovich, D.I.; Ostrand-Rosenberg, S.; Bronte, V. Coordinated regulation of myeloid cells by tumours. Nat. Rev. Immunol. 2012, 12, 253–268.
88. Law, A.M.K.; Valdes-Mora, F.; Gallego-Ortega, D. Myeloid-Derived Suppressor Cells as a Therapeutic Target for Cancer. Cells 2020, 9, 561.
89. Al-Khami, A.A.; Rodriguez, P.C.; Ochoa, A.C. Metabolic reprogramming of myeloid-derived suppressor cells (MDSC) in cancer. Oncoimmunology 2016, 5, e1200771.
90. Loftus, R.M.; Finlay, D.K. Immunometabolism: Cellular Metabolism Turns Immune Regulator. J. Biol. Chem. 2016, 291, 1–10.

91. Robinson, J.M.; Karnovsky, M.L.; Karnovsky, M.J. Glycogen accumulation in polymorphonuclear leukocytes, and other intracellular alterations that occur during inflammation. J. Cell Biol. 1982, 95, 933–942.
92. Srivastava, M.K.; Sinha, P.; Clements, V.K.; Rodriguez, P.; Ostrand-Rosenberg, S. Myeloid-derived suppressor cells inhibit T-cell activation by depleting cystine and cysteine. Cancer Res. 2010, 70, 68–77.