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Review

Metabolic Modulation of Immunity: A New Concept in Cancer Immunotherapy

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Immunotherapy shifted the paradigm of cancer treatment. The clinical approval of immune checkpoint blockade and adoptive cell transfer led to considerable success in several tumor types. However, for a significant number of patients, these therapies have proven ineffective. Growing evidence shows that the metabolic requirements of immune cells in the tumor microenvironment (TME) greatly influence the success of immunotherapy. It is well established that the TME influences energy consumption and metabolic reprogramming of immune cells, often inducing them to become tolerogenic and inefficient in cancer cell eradication. Increasing nutrient availability using pharmacological modulators of metabolism or antibodies targeting specific immune receptors are strategies that support energetic rewiring of immune cells and boost their anti-tumor capacity. In this review, we describe the metabolic features of the diverse immune cell types in the context of the TME and discuss how these immunomodulatory strategies could synergize with immunotherapy to circumvent its current limitations.

Immune checkpoint blockade (ICB) has transformed cancer treatment. Antibodies targeting the inhibitory T cell receptors CTLA-4 and PD-1 have significantly improved patient survival in many cases (Schadendorf et al., 2015), but numerous cancers remain refractory to this approach (Gauci et al., 2019). Some tumors lack immune cell infiltrates ("cold tumors"), rendering them unaffected by ICB (Fares et al., 2019). Other "hot tumors" contain immune cell infiltrates that support "immunoediting," in which cancer cells expressing neoepitopes are selected and resist the antigen-specific anti-tumor effector T cell (Teff cell) response. This resistance culminates in Teff cell exhaustion, which is closely related to metabolic changes in the tumor microenvironment (TME). The TME influences energy consumption and metabolic reprogramming in immune cells, often inducing them to become tolerogenic and inefficient in cancer cell eradication. In this review, we discuss how modulating the metabolism of immune cells ("immunometabolism") can improve the efficacy and durability of anti-tumor responses, boosting the success of anti-cancer immunotherapy.

Tumor Metabolism Shapes Anti-tumor Immune Responses

The TME contains cancer cells, immune cells, fibroblasts, blood vessels, extracellular matrix, and signaling molecules. The interplay among TME cell populations and their differing energetic needs shapes tumor development (Hanahan and Weinberg, 2011). To cope with their rapid proliferation, cancer cells implement a metabolic switch characterized by increased consumption of glucose and amino acids (AAs). Indeed, although they retain functional mitochondria and the capacity to engage oxidative phosphorylation (OXPHOS), cancer cells use glucose as their main energy source (Morais et al., 1994; Tan et al., 2015). Glucose and AAs are catabolized into carbon intermediates needed to assemble macromolecules, fuel ATP production in the electron transport chain (ETC), and help to maintain cellular redox capacity (Pavlova and Thompson, 2016).

A cancer cell's ability to increase its metabolic rate independently of external growth stimuli rests on its high mutational burden. Heterogeneity in the mutations exhibited by different cancer cells accounts for their distinct metabolic adaptations. Interestingly, excessive nutrient uptake by a tumor imposes metabolic stress on immune cells infiltrating the TME (Franchina et al., 2018b) (Figure 1). Glucose and glutamine deprivation prevent immune cells from switching from OXPHOS to glycolysis, compromising their function (see below). In addition, even in the presence of oxygen, glycolysis-derived pyruvate is not used to fuel the tricarboxylic acid (TCA) cycle in a tumor cell but is converted to lactate by lactate dehydrogenase (LDHA), a principle known as the Warburg effect (Warburg, 1956; Shim et al., 1997). The excess lactate produced by the proliferating cancer cells is exported by monocarboxylate transporters (MCTs) and increases the acidity of the TME (Halestrap, 2012), further interfering with immune cell metabolism (Renner et al., 2019). In melanoma patients, increased LDHA and lactate levels correlate with reduced survival (Brand et al., 2016). Moreover, lactate promotes tumor angiogenesis because it stabilizes

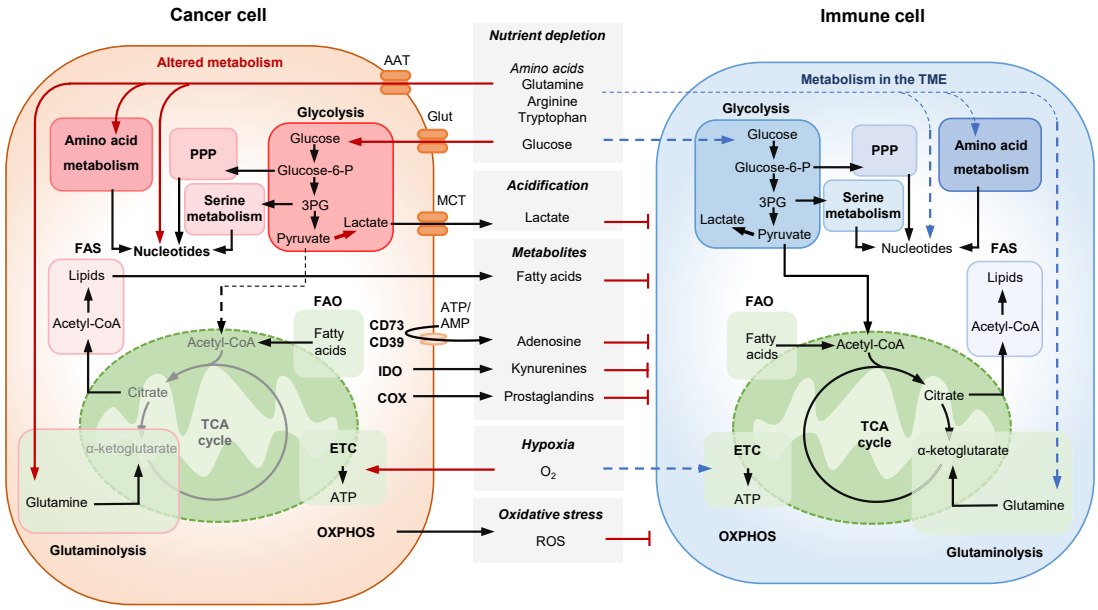


Figure 1. The Altered Metabolic Activity of Cancer Cells Affects the Energetic Rewiring of Immune Cells

In the tumor microenvironment (TME), metabolically highly active cancer cells interfere with immune cell function by depleting nutrients and producing immunosuppressive metabolites. Tumor cells consume large amounts of glucose and amino acids, including glutamine, arginine, and tryptophan, to fuel glycolysis, amino acid metabolism, and glutaminolysis. This activity limits the availability of these nutrients to immune cells in the TME. Increased glycolysis results in vigorous production of lactate, which acidifies the TME and suppresses immune cell effector functions. Tumor cells also release fatty acids, adenosine, kynurenines, and prostaglandins that repress immune cell effector functions. Increased oxygen consumption due to heightened OXPHOS contributes to hypoxia in the TME as well as release of ROS, which also inhibit immune cell anti-tumor functions. 3PG, 3-phosphoglyceric acid; AAT, amino acid transporters; acetyl-CoA, acetyl coenzyme A; AMP, adenosine monophosphate; ATP, adenosine triphosphate; COX, cyclo-oxygenase; ETC, electron transport chain; FAO, fatty acid oxidation; FAS, fatty acid synthesis; glucose-6-P, glucose 6 phosphate; Glut, glucose transporters; IDO, indoleamine 2,3-dioxygenase; MCT, monocarboxylate transporters; OXPHOS, oxidative phosphorylation; PPP, pentose phosphate pathway; ROS, reactive oxygen species; TCA, tricarboxylic acid.

hypoxia-inducible factor 1-alpha (Hif1α), which supports cancer cell survival under the hypoxic conditions often found in the TME. Hif1α also activates nuclear factor kappa B (NF-κB) in stromal cells and their secretion of vascular endothelial growth factor (VEGF) (Sonveaux et al., 2012; Végran et al., 2011). Neoangiogenesis is then induced and sustains tumor growth and invasion. In addition, Hif1α promotes the expression of ligands for PD-1 and CTLA-4 on cancer cells. These ligands deliver an inhibitory signal to Teff cells that suppresses their anti-tumor functions.

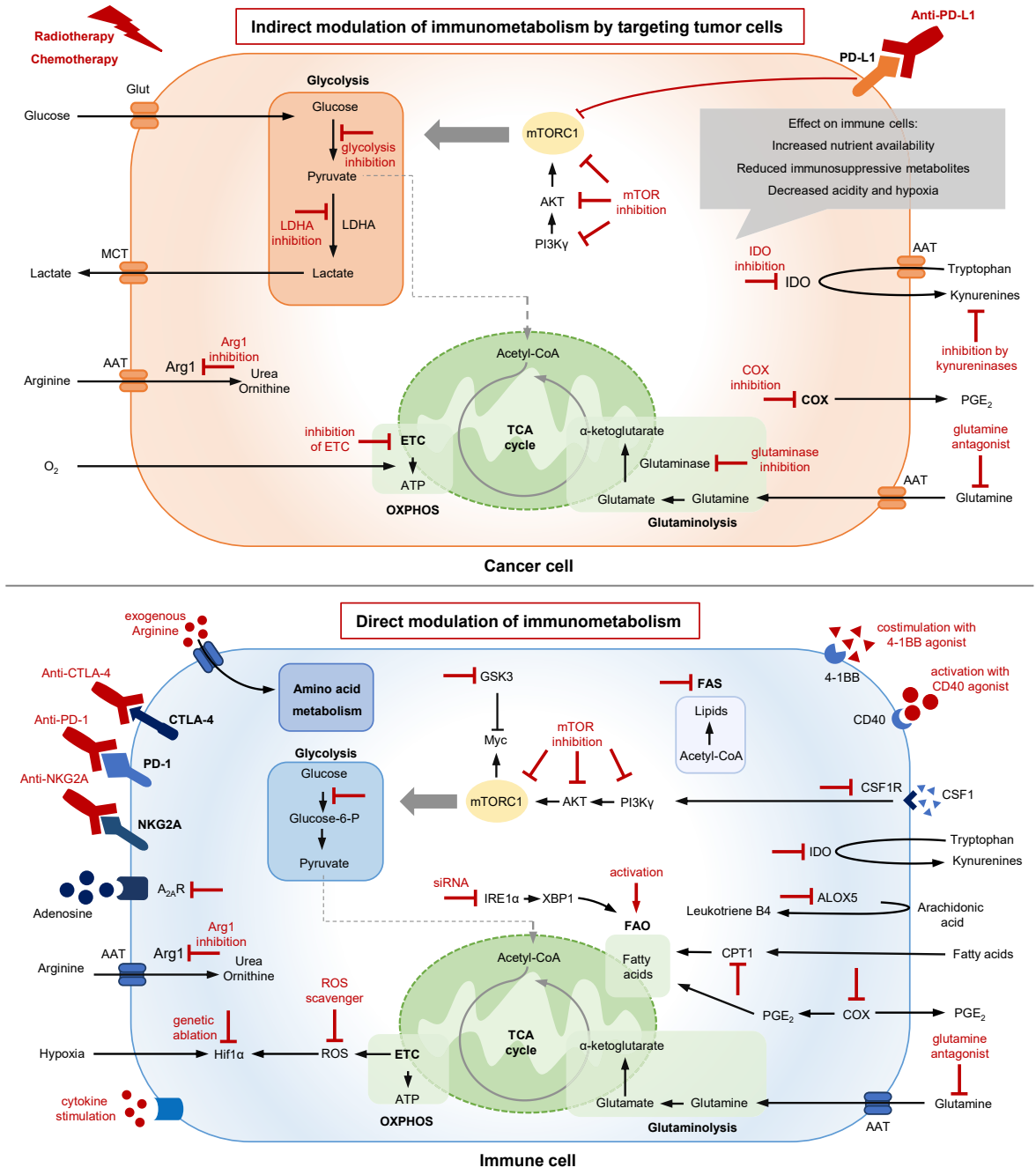
Besides glucose and glutamine, a solid tumor often consumes tryptophan. This AA is metabolized by indoleamine 2,3-dioxygenase (IDO) to kynurenine. Kynurenine not only promotes tumor cell survival and motility but also supports the generation of regulatory T cells (Treg cells), which suppress anti-tumor Teff cell responses. Increased IDO expression therefore correlates with tumor progression and poor prognosis (Liu et al., 2016).

Rapidly dividing cancer cells tend to accumulate reactive oxygen species (ROS). High levels of ROS are generally detrimental to normal cells. For example, accumulating ROS in T cells shuts down Teff cell responses by preventing the metabolic reprogramming that occurs upon activation (Mak et al., 2017). In contrast, malignant cells acquire potent antioxidant capacity that allows ROS to act as pro-tumorigenic signaling molecules (Reczek and Chandel, 2017; Harris et al., 2015) and to stabilize Hif1α (Chandel et al., 1998).

Although tumors share metabolic features that may appear to make them generally susceptible to therapeutic targeting, it has become evident that different types of cancers and even distinct regions of the same tumor show great heterogeneity and plasticity in their metabolic adaptations, allowing malignant cells to select for mechanisms that confer resistance to therapy (Kim and DeBerardinis, 2019). Thus, it may be wise to shift the targeting focus from the highly flexible tumor cell to a more-rigid player: the immune system. Although some immune-based strategies have proven to be powerful therapeutic alternatives to conventional cancer treatments, there remain several drawbacks. Improvements are needed to increase the efficacy of immunotherapy. Metabolic manipulation via genetic or pharmacological approaches may be a means of achieving this goal. Below, we review the main metabolic features of various immune cell types and describe how they are influenced by the TME. We also discuss current efforts to modulate these metabolic characteristics in order to improve cancer immunotherapy. These approaches may improve immune cell effector functions by themselves or through synergy with other metabolic modulators.

T Cells

T cells are major players in anti-tumor defense because they mount antigen-specific responses against cancer cells. Some activated T cells directly kill tumor cells by producing cytotoxic



Teff cell	Treg cell	NK cell	Macrophage	MDSC	DC	B cell
Anti-PD-1 Exogenous Arginine $A_{2A}R$ inhibition ROS scavenging Glycolysis inhibition Increased FAO 4-1BB costimulation glutamine antagonist	Anti-CTLA-4 IDO inhibition COX inhibition Arginase inhibition	Anti-NKG2A GSK3 inhibition Cytokine stimulation	CSF1R inhibition PI3Kγ inhibition Anti-PD-1	IDO inhibition CPT1 inhibition Epigenetic modulation	siRNA IRE1α-XBP1 FAS inhibition CPT1 inhibition mTOR inhibition Hif1α gene ablation Arginase inhibition	Activation with CD40 agonist ALOX5 inhibition

Figure 2. Indirect and Direct Strategies to Target Immunometabolism

Indirect strategies targeting tumor cell metabolism aim to increase nutrient availability to immune cells, reduce production of immunosuppressive metabolites, and decrease acidity and hypoxia in the TME. Inhibiting tumor cell glycolysis directly or indirectly, either by PD-L1 blockade or mTORC1 inhibition, reduces glucose consumption and lactate production. Lactate production can also be directly targeted by inhibition of LDHA. Blocking enzymes such as IDO, Arg1, and

(legend continued on next page)

components. Others secrete signaling molecules, such as cytokines, that activate or prime other types of immune cells.

Existing T-Cell-based Immunotherapies

The most successful cancer immunotherapy strategies to date are T-cell-based therapies, specifically ICB and adoptive cell transfer (ACT) (Figure 2). ICB aims to enhance anti-tumor T cell responses by using monoclonal antibodies (mAbs) to suppress the functions of T cell inhibitory receptors, such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) (ipilimumab) and programmed cell death-1 (PD-1) (nivolumab and pembrolizumab) (Hargadon et al., 2018). In the later stages of a physiological immune response, CTLA-4 becomes expressed mainly on activated T cells and interacts with the co-stimulatory molecules CD80 or CD86 on antigen-presenting cells (APCs) to block the acquisition of Teff cell function. The immune response is shut down before excessive collateral damage is inflicted on bystander cells. Ipilimumab prevents this shutdown of anti-tumor Teff cell activity, prolonging the response. PD-1 expressed on lymphocytes interacts with its ligands PD-L1 or PD-L2 expressed on cancer cells or tumor-associated macrophages (TAMs), promoting Teff cell exhaustion. Nivolumab and pembrolizumab interfere with this interaction, again extending Teff cell effectiveness. ICB is considered to be a great clinical success and is now approved for treatment of metastatic melanoma and tumors with genomic instability (e.g., colorectal carcinoma) (Hargadon et al., 2018).

ACT of T cells most often involves isolating autologous or allogenic T cells, improving their anti-tumor capacity, expanding their numbers in culture, and transferring them back to the patient. To increase ACT efficiency, engineered T cell receptors (TCRs) are created to direct T cells to a specific antigen and optimize their affinity (Rosenberg et al., 2008). The latest form of ACT is named ''chimeric antigen receptor'' (CAR) T cell therapy, in which the transferred T cells are engineered to express artificial antigen-binding receptors composed of an antigen-recognition site, a transmembrane region, and one or more co-stimulatory domains. CARs are histocompatibility leukocyte antigen (HLA) independent and circumvent tumor escape mechanisms. CAR T cell therapy has proven very effective against B cell malignancies, such as recurrent acute lymphoblastic leukemia (ALL) and chronic lymphocytic leukemia (CLL) (Hartmann et al., 2017). Nevertheless, CAR T cell therapy is associated with several severe side effects, including neurotoxicity, cytokine release syndrome (CRS), and some off-target effects (Hartmann et al., 2017; Lim and June, 2017). A major challenge with both ICB and ACT is the eventual development of T cell exhaustion and senescence, which prevent long-term Teff cell function and memory T cell development. Improving T cell fitness and longevity in the TME by metabolic stabilization could overcome these limitations, a goal that has prompted much recent basic research on T cell metabolism and its regulation.

Metabolic Differences in T Cell Subsets

The activation and differentiation of T cell subsets are highly dependent on metabolic status. Naive T cells are quiescent and produce ATP primarily by mitochondrial OXPHOS. Upon TCR engagement and co-stimulation, newly activated T cells undergo metabolic remodeling and switch to aerobic glycolysis, which produces ATP faster and drives macromolecule synthesis. Activated $CD4^+$ T cells differentiate into T helper cells, such as Th1, Th2, and Th17 cells, as well as Treg cells. Each subset requires distinct metabolic pathways to execute its functions. Both $CD4^+$ Th cells and $CD8^+$ Teff cells rely on glycolysis, express Glut1, and depend on mammalian target of rapamycin (mTOR) signaling to sustain their metabolic activity. In contrast, Treg cells express only low levels of Glut1, depend on fatty acid oxidation (FAO) (Macintyre et al., 2014; Michalek et al., 2011), and are negatively regulated by mTOR (Delgoffe et al., 2009; Delgoffe et al., 2011). In quiescent memory T cells, FAO favors longevity and provides energy to ensure a rapid switch to aerobic glycolysis for a fast secondary response upon recognition of the same antigen (Frauwirth et al., 2002; Michalek et al., 2011; Wang et al., 2011; van der Windt et al., 2013). The metabolic status of all these T cell subsets is crucial for their various anti-tumor functions, and it is becoming evident that the TME itself has a great influence on T cell metabolism, differentiation, and function. The modulation

glutaminase in cancer cells decreases amino acid depletion in the TME, although inhibition of IDO and COX interferes with the production of immunosuppressive molecules, such as kynurenines and prostaglandins, respectively. Kynurenines can also be directly inhibited by kynureninases. Glutamine antagonists decrease glutamine consumption by tumor cells and inhibit tumor metabolism. Pharmacological inhibition of the ETC in cancer cells can increase oxygen availability and reduce hypoxia. These strategies can be applied in addition to existing anti-cancer therapies, such as radiotherapy and chemotherapy. Direct strategies targeting immunometabolism aim to increase the fitness of immune cells and boost their anti-tumor activity. Inhibition of glycolysis or promotion of FAO in T cells as well as provision of exogenous arginine favor a memory phenotype with high anti-tumor activity. Also, glutamine antagonists favor a T cell memory phenotype by inducing metabolic reprogramming. 4-1BB co-stimulation can improve T cell proliferation and persistence. Inhibition of adenosine or ROS signaling through $A_{2A}R$ or ROS scavengers, respectively, reduces the immunosuppressive effects of these molecules on T cells. Blocking CTLA-4, IDO, COX, or Arg1 inhibits Treg cell formation and thus renders the TME less suppressive. In NK cells, inhibiting GSK3 prevents Myc degradation and increases NK effector functions. Cytokine stimulation of NK cells *in vitro* confers a memory phenotype with increased persistence after adoptive cell transfer. In macrophages, inhibition of CSF1R promotes the accumulation of pro-inflammatory macrophages in the TME. To inhibit the suppressive capacity of MDSCs, IDO inhibition, epigenetic modulation, and inhibition of fatty acid metabolism through CPT1 blockade have been proposed. In DCs, lipid metabolism is targeted because lipid accumulation impairs DC function. CPT1 and FAS inhibition as well as application of siRNA against the IRE1α-XBP1 signaling pathway can achieve this goal. Genetic ablation of Hif1α or inhibiting mTOR and Arg1 also reduce the suppressive phenotype of DCs in the TME. For B cells, CD40-mediated activation increases their capacity to activate cytotoxic T cells. Inhibition of enzymes promoting Breg cell differentiation, such as ALOX5, may decrease Breg cell frequencies in the TME. All these strategies can be applied in combination with ICB mediated by anti-CTLA or anti-PD-1 for T cells or anti-NKG2A for NK cells. $A_{2A}R$, adenosine receptor; AKT, protein kinase B; ALOX5, arachidonate 5-lipoxygenase; Arg1, arginase 1; CPT1, carnitine palmitoyl transferase 1; CSF1, colony stimulating factor 1; CSF1R, colony stimulating factor 1 receptor; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DC, dendritic cell; GSK3, glycogen synthase kinase 3; Hif1α, hypoxia inducible factor 1 α; IRE1α, inositol requiring kinase enzyme 1α; LDHA, lactate dehydrogenase; MDSC, myeloid-derived suppressor cells; mTORC1, mammalian target of rapamycin complex 1; NK, natural killer; O2, oxygen; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1; PGE2, prostaglandin E2; PI3Kγ, phosphatidylinositol 3-kinase γ; siRNA, small interference RNA; XBP1, X-box binding protein 1.

of various metabolites in the TME to boost anti-tumor responses is addressed in the next sections.

Glucose

The voracious consumption of glucose by cancer cells restricts its availability to normal cells in the TME. Using a sarcoma model, Chang et al. (2015) showed that excessive glucose uptake by tumor cells decreased the anti-cancer activity of tumor-infiltrating lymphocytes (TILs) in a manner linked to reductions in mTOR activity, glycolytic capacity, and interferon γ (IFNγ) production. In a glucose-deprived setting, $CD8^+$ T cells express lower levels of the essential anti-tumor effector molecules perforin and granzymes B and C (Cham et al., 2008). Glucose restriction in the TME can induce T cell anergy or even apoptosis through the Noxa/Mcl-1 axis (Alves et al., 2006; Zheng et al., 2009).

From a therapeutic perspective, increasing glucose availability in the TME can restore IFNγ production by TILs. By using ICB against PD-L1 on tumor cells, mTOR signaling is inhibited within these cells and their glycolytic turnover is reduced. Anti-tumor Teff cells are then able to increase their glucose uptake and extend their response (Chang et al., 2015). In addition, to improve their function in low-glucose TME, Ho and colleagues (Ho et al., 2015) transferred genetically engineered tumor-specific $CD4^+$ and $CD8^+$ T cells to overexpress phosphoenolpyruvate carboxykinase (PCK1). PCK1 allows the accumulation of the glycolytic metabolite phosphoenolpyruvate (PEP), which sustains nuclear factor of activated T cells (NFAT) signaling and consequent activation. ACT of these metabolic-modulated T cells to tumor-bearing mice decreased tumor growth and improved survival (Ho et al., 2015).

On the other hand, in ACT, blocking glucose metabolism can have the opposite effect. Treatment of $CD8^+$ T cells during *ex vivo* expansion with 2-deoxyglucose (2-DG), a glucose analog that impedes glycolysis, enhances the generation of memory cells and anti-tumor function after transfer (Sukumar et al., 2013). Glucose availability also influences mTOR signaling and Treg cell differentiation (Delgoffe et al., 2009). High numbers of Treg cells are associated with poor prognosis in many cancers, and Treg cell depletion promotes effective anti-tumor immunity (Tanaka and Sakaguchi, 2017). Thus, metabolic adjustments, not only to boost Teff cell but also to suppress Treg cell differentiation, may prove beneficial and shall be adjusted according to the therapeutic context.

Amino Acids

Like glucose, AAs are heavily metabolized by tumor cells, limiting their availability to T cells in the TME. L-arginine depletion *in vitro* decreases the proliferation of activated T cells (Rodriguez et al., 2007). Conversely, arginine supplementation during *in vitro* T cell activation causes metabolism to switch from glycolysis to OXPHOS, promoting the differentiation of central memory-like T cells. The survival and anti-tumor activity of these cells was enhanced by arginine addition in the expansion medium (Geiger et al., 2016). From a therapeutic standpoint, arginine metabolism can be blocked by inhibitors of the arginase enzymes ARG1 that degrade this AA. Cancer cells, tolerogenic TAMs, dendritic cells (DCs), and Treg cells use ARG1 to catabolize arginine. Thus, inhibiting ARG1 in the TME would increase arginine availability for Teff cell function and improve anti-tumoral responses. Currently, ARG1 inhibitors are under clinical testing in combination with ICB (ClinicalTrials.gov ID NCT02903914).

Tryptophan is also of limited availability in the TME. Tryptophan degradation by IDO results in kynurenine accumulation, which inhibits Teff cell proliferation through activation of the aryl hydrocarbon receptor (AHR) (Opitz et al., 2011). IDO activity also leads to Treg cell generation (Mezrich et al., 2010), and blocking IDO converts these cells into non-suppressive Th17 cells (Sharma et al., 2009; Munn et al., 2005). Indeed, IDO inhibitors, such as 1-methyltryptophan, render the TME less immunosuppressive and promote tumor-specific Teff cell activation and proliferation. To increase tryptophan in the TME, the IDO1/2 inhibitors indoximod or epacadostat are currently being assessed in combination with ICB in clinical trials for melanoma or urothelial cancer, respectively (ClinicalTrials.gov ID NCT03361865 and NCT02073123). In addition, kynureninase can be used to directly degrade kynurenine. It synergizes with ICB to promote survival in murine melanoma and breast and colon carcinoma cell lines (Triplett et al., 2018).

Glutamine is another amino acid consumed by tumor cells in the TME and important to fuel the TCA cycle and the production of nucleotides and proteins. Limitation of glutamine or leucine inhibits Th1 and Th17 differentiation but does not affect Treg cells (Sinclair et al., 2013; Nakaya et al., 2014). Glutamine-deprived T cells exhibit impaired effector function (and so a defective anti-tumor response) and are less potent in inducing inflammatory disease (Nakaya et al., 2014). However, it has been shown that the use of a glutamine antagonist (6-diazo-5-oxo-L-norleucine [DON]) can impair tumor cell metabolism, which results in higher nutrient availability and decreased hypoxia in the TME and is accompanied with better anti-tumor therapy in combination with anti-PD1. Interestingly, although the use of glutamine antagonist, DON-derivative JHU083, disabled tumor metabolism, it increased infiltrating $CD8^+$ T cells and skewed them toward a long-lived, highly activated memory-like phenotype capable of effector function. The authors show that tumor cells have less plasticity during inhibition of glutamine metabolism, although T cells metabolically reprogram, which leads to higher survival, proliferation, and effector function. Glutamine blockage could thus be one possibility to differentially modulate cancer and immune cell metabolism (Leone et al., 2019).

Fatty Acids

The high metabolic activity of tumor cells demands increased fatty acid (FA) synthesis, and this increased lipid content in the TME can have varying effects on T cell subsets. Treg cells take up exogenous fatty acids to build up their suppressive function. Conversely, Th17 function relies on a glycolytic-lipogenic metabolism. Berod and colleagues (Berod et al., 2014) showed that pharmacological inhibition or genetic deletion of acetyl-coenzyme A (CoA) carboxylase (ACC1), which promotes FA metabolism, drives Treg cell differentiation while compromising Th17 development. The increased lipid content in the TME might contribute to further promote immune suppression by Treg cells, because they rely more on FAO (Michalek et al., 2011; Macintyre et al., 2014). On the other hand, it was also shown that a subset of $CD8^+$ T cells with increased lipid uptake upregulates PD-1 in cancer patients, which would normally suppress their function. Strikingly, upon treatment with PD-1 blockade, this subset had

a highly specific anti-cancer function, and its presence predicted an efficient anti-tumor response and better survival (Thommen et al., 2018). This clinical paradox shows the importance of validating basic research and finding biomarkers to improve therapeutic efficacy.

FAO seems to favor longevity in T cells, as for memory T cells. Therefore strategies increasing FAO could be favorable to generate a durable anti-tumor immunity. Increasing FAO by an agonist of the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α)/peroxisome proliferator-activated receptor (PPAR) pathway, benzafibrate, improved survival and proliferation of tumor-reactive cytotoxic T lymphocytes (CTLs) by blocking apoptosis and further reduced tumor volume in combination with anti-PD1 blockade. Interestingly, increasing FAO in CTLs *in vitro* also increased survival and proliferation, which could be promising for ACT strategies (Chowdhury et al., 2018).

The concept that T cells use glycolysis for effector functions and FAO for memory formation has been widely accepted. Carnitine palmitoyl transferase-1 (CPT1) is involved in the translocation of long-chain FAs from the cytosol to the mitochondrial matrix, where FAO occurs. Strikingly, using genetically modified mice harboring a T-cell-specific deletion of CPT1A, Raud et al. (2018) showed that CPT1A is not crucial for the establishment of either Treg cells or memory T cells, which differs from studies using the CPT1A inhibitor etomoxir. One possible explanation might be adaptations that can arise in genetic altered mutants; however, the work of Raud et al. (2018) and Divakaruni et al. (2018) indicate that etomoxir, when used at higher concentrations, engages different targets than CPT1A. Although it is non-debatable that etomoxir has immune-modulating effects, more comparative studies are required to clarify FAO's role in various T cell subsets. Importantly, Treg cells and memory T cells utilize various pathways to mobilize fatty acids and use short- or medium-chain FAs whose translocation is not dependent on CPT1A (Bachem et al., 2019; Field et al., 2020). Deeper deciphering of the effects of lipid content on specific T cell functions is needed to better modulate their anti-tumoral properties.

Oxygen

In addition to glucose, AAs, and lipids, tumor cells are keen consumers of oxygen, which leads to hypoxia in the TME. Under hypoxic conditions, Hif1α is increased in T cells and promotes Th17 cell differentiation, resulting in enhanced expression of Th17 signature genes, such as RORγT. Th17 cells can have regulatory or inflammatory properties, depending on the type of cancer and the nature of the activation stimulus (Bailey et al., 2014). Increased Hif1α also impairs the anti-tumor activity of $CD8^+$ TILs, as evidenced by the delay in tumor progression in mice transplanted with $CD8^+$ T cells in which Hif1α was knocked down (Zhang et al., 2017). The role of Hif1α in Treg cells is less clear. In one study, Hif1α decreased Treg cell differentiation by targeting Foxp3 for proteasomal degradation (Shi et al., 2011; Dang et al., 2011), but in another study, Hif1α enhanced Foxp3 in induced Treg cells and boosted their immunosuppressive function *in vivo* (Clambey et al., 2012). This riddle remains under investigation.

In the clinic, tumor cells in a hypoxic TME may be treated with metformin, a drug already used for diabetic patients. Metformin blocks oxygen consumption by cancer cells, rendering the TME less hypoxic. Metformin can synergize with PD-1 ICB to improve intra-tumoral T cell function and cancer clearance *in vivo* (Scharping et al., 2017). In a murine model, the administration of metformin also favored the generation of memory T cells, which resulted in better anti-tumor immunity (Pearce et al., 2009).

ROS

Oxygen is needed to produce ROS during mitochondrial respiration (Franchina et al., 2018b). Moderate levels of ROS are essential for normal T cell function because they activate NFAT, which leads to antigen-specific T cell expansion (Sena et al., 2013). Thus, in the hypoxic TME, the production of intracellular ROS in TILs can be insufficient. Indeed, TILs show decreased mitochondrial function and mass that are accompanied by loss of ROS production. Reprogramming these TILs to favor mitochondrial biogenesis enhanced their anti-tumor activity and improved survival in a mouse tumor model (Scharping et al., 2016).

Despite the above findings, ROS are actually often increased in the TME. ROS can act as signaling molecules and induce cell activation, namely through the mitogen-activated protein kinase (MAPK) pathway. In the cancer cells, ROS can also induce transcription factors, such as Hif1α, that in turn increase the expression of genes important for vascularization, like VEGF. This leads to enhanced angiogenesis in the TME and increased survival and proliferation of tumor cells (Weinberg et al., 2019). On the contrary, ROS seem to have a detrimental effect for T cells. Our group has shown that rising ROS levels in T cells need to be balanced by antioxidants. High ROS levels impair metabolic reprogramming in T cells by hindering proper activation of mTOR, NFAT, and Myc and the establishment of Teff functions (Mak et al., 2017).

In addition, our group has recently shown that Treg cells contain significantly higher cellular concentrations of the antioxidant glutathione (GSH), which renders them more resistant to increasing ROS (Kurniawan et al., 2020). This ensures their suppressive function, although conventional T cells might be inactivated already at lower environmental ROS. It is well likely that increased ROS in the TME contributes to the establishment of a tolerogenic environment by inactivating Teff cells and, in parallel, these ROS concentrations are not able to interfere with Treg cell function. Accordingly, $CD8^+$ TILs isolated from patients with renal cell carcinoma contained dysfunctional mitochondria and produced large amounts of ROS. These TILs showed defects in activation, proliferation, and metabolism that could be partially restored by ROS scavengers (Siska et al., 2017). Culturing naive $CD8^+$ T cells with the ROS scavenger N-acetyl cysteine (NAC) increases the formation of T memory stem cells capable of prolonged tumor control (Pilipow et al., 2018). Interestingly, these cells demonstrated increased persistence, which are key factors underpinning the durability and efficacy of immunotherapy. In mouse tumor models, the transfer of less-differentiated $CD8^+$ T cells, such as naive or memory T cells, increased survival rates compared to the transfer of Teff cells (Klebanoff et al., 2011). Of note, also mitochondrial ROS inhibitors, such as ME-344 inhibiting mitochondrial complex I, are currently being evaluated in a clinical trial with breast cancer patients (ClinicalTrials.gov ID NCT02806817; Weinberg et al., 2019). These findings

underscore the importance of controlling ROS in T cells to allow the metabolic remodeling needed to establish Teff cell functions and memory (Franchina et al., 2018b; Mak et al., 2017). Although, Treg cells are more resistant to oxidative stress when compared to effector T cells and contain high GSH, their functionality also depends on their redox state. Genetic ablation of the synthesis of GSH increases the metabolic activity of Treg cells, which lowers Foxp3 expression and impairs their suppressive activity. Removing this ROS-defense mechanism in Treg cells significantly increases anti-tumor immunity (Kurniawan et al., 2020).

However, in Teff cells, ROS scavenging or inhibition could improve expansion and proliferation of these cells in the TME, which would be beneficial in existing T-cell-based immunotherapies, such as ICB.

ATP

Extracellular ATP concentrations are elevated within a tumor mass due to its hypoxic and inflammatory environment and its high levels of cellular necrosis and apoptosis. This ATP is sequentially catabolized to adenosine by the ectonucleotidases CD39 and CD73, which are expressed both by tumor cells and myeloid-derived suppressor cells (MDSCs) (see below) (Vigano et al., 2019). Adenosine accumulating in the TME has an immunosuppressive effect on T cells because it signals via the A_{2A} extracellular adenosine receptor ($A_{2A}R$) to inhibit the interleukin-2 (IL-2) upregulation and proliferation induced by TCR stimulation (Huang et al., 1997). $A_{2A}R$ engagement also expands Treg cells and increases their immunosuppressive activity (Ohta et al., 2012; Maj et al., 2017). Inhibition of adenosinergic signaling by the $A_{2A}R$ inhibitor CPI-144 (in combination with ICB) is currently under investigation in patients with refractory renal cell carcinoma (ClinicalTrials.gov ID NCT02655822).

Lactate

Highly glycolytic tumor cells release lactate into the TME, whose accumulation leads to TME acidification. Work using a murine melanoma model showed that this lactic acid interferes with T cell survival and activation (Brand et al., 2016). Through NFAT downregulation, lactate inhibits IFNγ expression and curtails the anti-tumor response, allowing cancer growth and immune evasion. The motility of $CD4^+$ and $CD8^+$ T cells is inhibited by lactate metabolites (Haas et al., 2015), perhaps compromising the ability of TILs to infiltrate tumors or find their way to draining lymph nodes (LNs) for activation. Pharmacological inhibition of the lactate transporters MCT1 or MCT4 to minimize the immunosuppressive effects of lactic acid in the TME has shown promise in a mouse tumor model. Mice treated with diclofenac, a nonsteroidal anti-inflammatory agent already used in the clinic and identified as a MCT inhibitor, showed improved survival when also treated with ICB (Renner et al., 2019). Similarly, knockdown of LDHA in mouse tumor cells by interference RNA nanoparticles neutralized TME acidity and promoted tumor infiltration by $CD8^+$ T cells and natural killer (NK) cells while decreasing the number of immunosuppressive immune cells (Zhang et al., 2019). This neutralization of TME pH also potentiated ICB. These results reinforce an earlier report showing that buffering a tumor's pH with bicarbonate therapy impairs cancer growth in some mouse tumor models and increases T cell infiltration (Pilon-Thomas et al., 2016).

Prostaglandin E2

Prostaglandin E2 (PGE_2) is a bioactive lipid metabolite synthesized by cyclo-oxygenase (COX). Once secreted into the TME by tumor cells, PGE_2 has immunosuppressive effects. PGE_2 signaling enhances Treg cell Foxp3 expression and activity, enhancing tumor growth (Sharma et al., 2005). PGE_2 may also inhibit IL-2 and IFNγ production by $CD4^+$ T cells (Snijdewint et al., 1993). Clinical trials combining ICB with COX1/2 inhibitors, including acetylsalicylic acid (Aspirin), are currently under way (ClinicalTrials.gov ID NCT03638297).

The above studies illustrate how the TME alters T cell fitness. Clarifying the energetic and nutritional needs of each T cell subset and defining precisely how these are regulated in the TME is crucial for progress in cancer immunotherapy. Rational modulation of T cell metabolism could facilitate combination with other approaches (like ICB) to increase the anti-tumor efficacy and persistence of these T cells in cancer patients.

NK Cells

Cancer immunotherapy is not limited to T cells; manipulation of NK cells has also been successful. NK cells exert cytotoxic capacity without prior sensitization. Due to their capacity to rapidly produce effector molecules, they are key players in the acute response against malignant cells. NK cell activation is determined by a balance between activating and inhibitory receptors (Miller and Lanier, 2019). Thus, as is true for T cells, informed modulation of NK cell metabolism may lead to improved strategies for cancer immunotherapy.

Glucose and Amino Acids

Resting NK cells show only low levels of both glycolysis and OXPHOS, but even at these reduced rates, the glycolytic and oxidative programs are crucial for their rapid effector responses (Keppel et al., 2015). Upon activation by receptor engagement or cytokines, NK cells upregulate glucose and nutrient transporters, induce glycolytic enzymes, and increase mitochondrial mass to sustain increased OXPHOS and achieve maximum respiratory capacity. Inhibition of OXPHOS or glycolysis by oligomycin or 2-deoxyglucose reduces IFNγ and granzyme B production and impairs NK cytotoxicity (Donnelly et al., 2014; Keating et al., 2016). Defects in NK function also occur upon inhibition of the AA transporters SLC1A5 and CD98 (Jensen et al., 2017). The improved metabolic capacity is regulated by mTOR activation (Marçais et al., 2014; Donnelly et al., 2014; Keating et al., 2016; Jensen et al., 2017). Thus, as mTOR is a nutrient sensor, when AAs are scarce, such as in the TME, NK anti-tumor function may be compromised.

Interestingly, glycolysis-derived pyruvate that enters the mitochondria of an NK cell does not participate in the TCA cycle. Instead, this pyruvate is converted to citrate and exported to the cytosol in exchange for malate via the citrate-malate shuttle (CMS), concomitantly generating NADH to fuel OXPHOS and ATP production. The CMS also produces NAD^+, which serves as a cofactor for glyceraldehyde-3-phosphate dehydrogenase (GAPDH) during glycolysis induction. CMS activity in NK cells is regulated by sterol-regulatory-element-binding protein (SREBP). Increased mTORC1 signaling upon NK cell activation drives SREBP upregulation and thereby induces key factors of the CMS. Consequently, SREBP inhibition impairs NK cell IFNγ

production and cytotoxicity (Assmann et al., 2017). Because the CMS is exclusively fueled by glucose, NK cells do not use glutamine to drive OXPHOS. Nevertheless, glutamine is important for c-Myc signaling, which upregulates glucose transporters and glycolytic enzymes, and induces mitogenesis to support increased OXPHOS (Loftus et al., 2018).

The fact that NK cells, unlike cancer cells, do not need glutaminolysis to feed their energetic needs offers a therapeutic opportunity. CB-839 is a glutaminase inhibitor currently in clinical trials for various solid tumors (ClinicalTrials.gov ID: NCT02071862 and NCT02861300). CB-839 inhibits glutamine usage by tumors, blocking their energy production. In addition, by increasing glutamine availability, CB-839 may boost mTOR and c-Myc signaling in NK cells and so their cytotoxic capacity. Another approach uses glycogen synthase kinase-3 (GSK3), which inhibits Myc degradation, to sustain NK effector functions (Gardiner, 2019; Terrén et al., 2019).

Fatty Acids

Whether FAO is needed to fuel the TCA cycle in activated NK cells is unclear. Studies with the CPT1A inhibitor etomoxir show that NK cells do not depend on this oxidative pathway to sustain their energetic needs and function (Marçais et al., 2014). However, as mentioned above, etomoxir has CPT1A-independent effects at higher concentrations, and some of these conclusions should be re-evaluated by alternative approaches (Raud et al., 2018; Divakaruni et al., 2018). Nevertheless, accumulation of intracellular lipids in NK cells reduces metabolic activity and impairs effector function (Michelet et al., 2018). Certain metabolites of cholesterol, including 25-hydroxycholesterol and 27-hydroxycholesterol, inhibit SREBP function and so disrupt NK metabolism and effector functions (Assmann et al., 2017).

TME-Associated Immunosuppression

NK cells in the TME are subjected to numerous immunosuppressive factors. As noted above, tumor-cell-mediated depletion of glucose and glutamine inhibits mTOR signaling and Myc-sustained glycolysis (Loftus et al., 2018). Transforming growth factor β (TGF-β) directly suppresses NK metabolism through mTOR inhibition (Viel et al., 2016; Zaiatz-Bittencourt et al., 2018). TGF-β also induces fructose-1,6-bisphosphatase 1 (FBP1) in tumor-infiltrating NK cells, reducing glycolysis and effector functions (Cong et al., 2018). Acidity in the TME decreases mitochondrial mass and induces ROS in tumor-resident NK cells. This impairs NK cytotoxicity and IFNγ production (Harmon et al., 2019; Brand et al., 2016; Pötzl et al., 2017). Adenosine in the TME reduces NK cell function because its engagement of $A_{2A}R$ inhibits glycolysis and OXPHOS (Chambers et al., 2018). Furthermore, nitric oxide (NO) and kynurenine in the TME interfere with NK antibody-dependent cellular cytotoxicity and cytokine production, respectively (Stiff et al., 2018; Frumento et al., 2002). Hypoxia in the TME sustains the activation of a complex formed by mTORC1 and dynamin-related protein 1 (mTORC1-Drp1) in NK cells, which induces mitochondrial fission, leading to reduced OXPHOS and NK killing efficiency (Zheng et al., 2019). However, IL-15-primed human NK cells show increased expression of glycolytic genes when cultured under hypoxic conditions for a short period (Velásquez et al., 2016). Thus, the relationship between NK cell function and hypoxia must be studied in a context-dependent manner.

ICB and ACT

As is true for T cells, metabolic modulation of NK cells in the TME can be achieved by antibodies against inhibitory checkpoints (Dao and Matosevic, 2019). Exhausted and impaired NK cells express high levels of NKG2A, an inhibitory receptor. Engagement of NKG2A impairs mTOR signaling and IFNγ production (Sun et al., 2016), and mAb-mediated blocking of NKG2A signaling improves NK-mediated immunity. In mouse tumor models, NKG2A blockade synergizes with anti-PD1 ICB and reduces tumor growth. In humans, clinical trials with the anti-NKG2A mAb monolizumab are ongoing (ClinicalTrials.gov ID NCT02671435 and NCT02643550; André et al., 2018). Given the plethora of inhibitory receptors expressed by NK cells, many possibilities for checkpoint modulation likely exist. Conversely, mAbs engaging NK-cell-activating receptors may boost their metabolism and function.

ACT of NK cells can be effective, and expansion of primary or immortalized NK cells under conditions of metabolic modulation has yielded promising results. NK cells cultured in the presence of a GSK3 inhibitor before transfer to the patient show an increased cytotoxic capacity. The short-term pre-culture with a compound that inactivates GSK3 allows specific action on NK cells and circumvents the side effects of this drug, such as $CD8^+$ T cell inhibition and Treg cell recruitment (Parameswaran et al., 2016). Pre-activation of NK cells by incubation with IL-12/15/18 heightens their cytotoxicity and results in a memory-like phenotype, increasing NK cell persistence (Ni et al., 2012). Finally, genetically engineered expression of NK activating receptors by ACT NK cells rewires their metabolism to support effector functions and resistance to immunosuppression in the TME (Hu et al., 2019).

Macrophages

Macrophages constitute the largest population of myeloid cells infiltrating human solid tumors. The presence of macrophages in the TME correlates with higher tumor grade and shorter patient survival (Gentles et al., 2015; Gautier et al., 2012). These TAMs respond to environmental cues that compel them to polarize toward either a pro-inflammatory state or tolerogenic phenotype (Pathria et al., 2019). TME metabolic niche can drive development of more tolerogenic macrophages. By unravelling the metabolic pathways involved in macrophage polarization, researchers hope to design strategies to repolarize tolerogenic TAMs back to a pro-inflammatory, tumoricidal state, thereby improving the assault on the cancer.

Glucose and Fatty Acids

Pro-inflammatory TAMs are highly glycolytic and produce large amounts of lactate. They also have heightened tumoricidal functions due to their elevated ROS production (MacMicking et al., 1997). Tolerogenic TAMs maintain an oxidation-driven metabolism that increases tumor vascularization and disease progression. TAMs in hypoxic tumor regions show increased expression of Hif1α and its target REDD1. REDD1 inhibits mTOR signaling and decreases glucose intake by macrophages, allowing endothelial cells greater access to glucose. The neoangiogenic process increases along with metastatic potential

(Wenes et al., 2016). Even under normoxic conditions, human TAMs show decreased GAPDH and succinate dehydrogenase (SDH) expression, which is crucial for mitochondrial oxidation and ROS generation. Lack of glycolysis and ROS leads to suppression of anti-tumor activity (Miller et al., 2017; Mills et al., 2016).

The above pro-inflammatory versus tolerogenic TAM paradigm does not hold true for every tumor since macrophages are metabolically flexible and difficult to categorize. Sometimes glycolysis can sustain an immunosuppressive phenotype in TAMs if tumor-derived lactate causes them to rewire to glycolysis (Colegio et al., 2014). This glycolysis then further increases the secretion of lactate, tumor necrosis factor (TNF), and IL-6 into the TME (Arts et al., 2016; Zhao et al., 2017). High lactate and low pH in the TME drives the generation of tolerogenic macrophages with high levels of arginase (Bohn et al., 2018; Carmona-Fontaine et al., 2017). Arginase decreases CD3ξ chain expression in T cells, contributing to immunosuppression (Rodriguez et al., 2004). Accordingly, genetic deletion of LDHA, 2-DG administration, or mTORC1 inhibition have been proposed as therapeutic avenues designed to decrease glycolytic metabolism in cancer cells, reduce lactate in the TME, and repolarize TAMs to a pro-inflammatory state. Similarly, anti-PD-L1 immunotherapy reduces glycolysis in tumor cells and so might indirectly induce TAM repolarization by increasing glucose availability (Vitale et al., 2019).

Tolerogenic TAMs in the TME also engage in glutaminolysis, depleting the glutamine needed by anti-tumor T and NK cells. In addition, the consequent limited availability of α-ketoglutarate affects macrophage epigenetic reprogramming, which is intrinsically related to metabolic control (Liu et al., 2017).

Immunosuppressive TAMs show increased FAO, in line with their heightened oxidative metabolism. FAO sustains IL-10 secretion, which promotes tumor progression (Vats et al., 2006; Park et al., 2015).

MDSCs

Just like macrophages, MDSCs are myeloid cells that become "corrupted" and accumulate in the TME, where they exert immunosuppression via various mechanisms. In chronic inflammatory state, as it is the case of cancer, myeloid cells are recruited from the bone marrow without completing differentiation. They migrate to the TME under the influence of CCL2 and acquire suppressive capacity (Groth et al., 2019). *Ex vivo*, the differentiation of murine MDSCs relies on tumor-derived factors, such as granulocyte-macrophage colony stimulating factor (GM-CSF) and IL-6. Immunosuppressive factors secreted in the TME, such as PGE_2, IL-10, IL-1β, TGF-β, and VEGF, also contribute (Lechner et al., 2010). IDO-expressing MDSCs then accumulate mainly in hypoxic tumor regions (Chiu et al., 2017; Chun et al., 2015; Holmgaard et al., 2015).

Once established in the TME, MDSCs secrete immunosuppressive cytokines, such as TGF-β and IL-10, that recruit Treg cells, directly suppress Teff cells, and promote tolerogenic TAM polarization (Beury et al., 2014; Schlecker et al., 2012). Hypoxia and lactate in the TME induce Hif1α stabilization in MDSCs, culminating in expression of PD-L1 that engages PD-1 to shut down anti-tumor Teff cells.

Glucose and Fatty Acids

FAO seems to sustain MDSC immunosuppressive capacity (Yan et al., 2019; Hossain et al., 2015). MDSCs switch from glucose to lipid metabolism via controlled mTOR inhibition and induced PPARγ expression, a lipid sensor and transcriptional regulator of lipid metabolism. The increased lipid content in the TME induces MDSCs to express the FA transporters CD36 and CD204. Hence, MDSCs of cancer patients tend to accumulate more lipids than their counterparts in healthy controls (Yan et al., 2019). Mitochondrial biogenesis and oxygen consumption increase, as well as expression of CPT1 and HADHA, enzymes essential for FAO in the mitochondria. FAO then induces ARG1, NO, and peroxynitrite, resulting in Teff cell death (Hossain et al., 2015). Inhibition of lipid metabolism by a genetic approach caused murine MDSCs to switch to glycolysis, enhancing their proliferation but inhibiting their suppressive functions (Ding et al., 2014). The therapeutic relevance of inhibiting glycolysis or FAO in MDSCs has thus been investigated. Pharmacological approaches using ranolazine interfere with MDSC suppressive capacity (Hossain et al., 2015). Diminishing hypoxia in the TME and removing glycolysis-derived immunosuppressive metabolites might also neutralize resident MDSCs.

ROS

To sustain their tolerogenic function, MDSCs activate NADPH oxidases (NOX) to produce high ROS. Accordingly, inhibition of ROS generation impairs MDSC suppressive capacity (Corzo et al., 2009). High ROS induce VEGF and neoangiogenesis and drive MDSC recruitment to the TME (Kusmartsev et al., 2008). Increased ROS are often accompanied by elevated NO. MDSCs express high levels of NO synthase (iNOS), and NO production induces COX2 that promotes PGE_2 production, culminating in expression of IDO, ARG1, IL-10, and VEGF. Arginine, tryptophan, and cysteine are thus depleted in the TME, compromising T cell function (Sica et al., 2017). Importantly, MDSCs are protected from death caused by tumor- and self-derived ROS by induction of the master antioxidant transcription factor Nrf2. MDSCs can also increase glycolysis to accumulate phosphoenolpyruvate (PEP), which is a ROS scavenger (Ohl et al., 2018). MDSCs can be targeted directly and rendered less suppressive by IDO, NOX, or Nrf2 inhibitors (Sica et al., 2017).

ICB

In theory, strategies that inhibit the energetic and suppressive properties of MDSCs can be combined with ICB to boost the anti-tumor functions of Teff cells. In a mouse model of melanoma, metformin used to block OXPHOS in MDSCs synergized with PD-1 ICB to improve Teff cell function and drive tumor clearance (Kim et al., 2017). Currently, a phase 2 clinical trial is ongoing to test the efficacy of combining metformin and anti-PD1 in human lung cancer (ClinicalTrials.gov ID NCT03048500). Similarly, a combination of ICB and IDO inhibition is currently under clinical investigation in melanoma patients (ClinicalTrials.gov ID NCT02073123). In metastatic mouse tumors, epigenetic modulation plus ICB has proven effective in suppressing MDSCs. The use of azacitidine (DNA methyltransferase inhibitor) and entinostat (histone deacetylase inhibitor) in combination with anti-PD-1 and anti-CTLA4 antibodies has shown pre-clinical benefits and is under clinical testing (ClinicalTrials.gov ID NCT01928576). This epigenetic modulation is thought to influence the metabolic

status of MDSCs (Kim et al., 2014). More research is needed to resolve MDSCs metabolic properties in order to counteract their suppressive effect on anti-tumor immunity.

Neutrophils

Neutrophils can exert both supporting and suppressing influences on the anti-tumor response. Recent discoveries have revealed a great metabolic plasticity of these myeloid cells. This energetic flexibility might explain their conflicting roles in the TME and help designing new therapeutic strategies.

Neutrophils can impede tumor growth through direct cytotoxicity or by presenting cancer antigens to anti-tumor T cells (Coffelt et al., 2016). However, neutrophils are also induced to become suppressive. Neutrophils' release of ROS and arginase 1 hinders cell cycle progression and arrests T cell proliferation *in vitro* (Lecot et al., 2019). A higher neutrophil count (neutrophil-to-lymphocyte ratio [NLR]) in the blood of cancer patients is often associated with poor disease prognosis (Templeton et al., 2014). This effect has been shown to be relevant to the success of ICB, where a low NLR correlated with improved response to treatment (Capone et al., 2018).

How then are neutrophils subverted in the TME? High TGF-β levels and a specific milieu of molecules (chemokines, PGE_2, and IDO, for example) attract neutrophils to establish in the tumor bed and acquire an immunosuppressive phenotype. Tumor-associated neutrophils seem to contain less cytotoxic granules and produce lower amounts of ROS, crucial for cytotoxic activity. Pro-tumor neutrophil subpopulations that interact with tumor-circulating cells and foster the metastatic process have been described. They produce angiogenic factors and matrix-degrading enzymes (Lecot et al., 2019).

From a metabolic point of view, circulating neutrophils have always been described to preferably engage glycolysis and pentose phosphate pathway (PPP) to perform their cytotoxic functions. However, this perspective has been recently challenged in the context of tumorigenesis. It has become increasingly clear that neutrophils comprise an extremely heterogeneous population with remarkable metabolic flexibility. For instance, Rice et al. (2018) have reported that immature c-Kit$^+$ neutrophils are able to engage oxidative mitochondrial metabolism when glucose levels are low. This group described that tumor-elicited c-kit signaling in neutrophils triggers their use of FAO to drive NADPH-dependent ROS production and that these sustained ROS levels suppress the functions of anti-tumor CD8$^+$ T cells. Neutrophils with an oxidative profile are also found circulating in peripheral blood of cancer patients. Rice et al. (2018) used a genetic approach to silence c-kit ligand expression by tumor cells and observed reductions in both neutrophil oxidative metabolism and suppressive activity in the TME. Bolstering these findings, Hsu et al. (2019) described immature low-density neutrophils (iLDNs) that rely on proline and glutamate catabolism to support mitochondrial-dependent ATP production. The group used a mouse model of breast cancer, where, in a glucose-deprived environment like the TME, iLDNs were found to exert pro-metastatic functions. This subpopulation was able to create extracellular traps (NETosis), a cytotoxic process performed by neutrophils, which was thought to be uniquely dependent on glycolysis (Hsu et al., 2019).

These recent discoveries shed light on the ability of immune-suppressive players to adapt their metabolism to distinct nutrient availability scenarios. One strategy to circumvent this flexibility might be to inhibit the production of suppressive molecules, such as PGE_2, IDO, or ROS. More translational research is needed to unravel mechanisms of neutrophil metabolism and devise means of repolarizing these cells toward anti-tumor functions.

Eosinophils

Eosinophils are terminally differentiated granulocytes that, like neutrophils, have a controversial role in tumor control. Tumor-associated eosinophils have been described in a variety of different cancers, but whether their presence promotes or suppresses tumorigenesis appears to vary by context (Reichman et al., 2016). The same conundrum holds true for the prognostic value of eosinophilia in the outcome of cancer immunotherapy. In one study of cancer patients treated with ICB, an increased absolute eosinophil count was associated with extended patient survival (Delyon et al., 2013). However, in another study, the accumulation of eosinophils upon anti-CTLA-4 treatment was found to predict the development of immune-related adverse events (irAEs) (Schindler et al., 2014).

Carretero et al. (2015) showed that activated eosinophils within the TME are able to normalize the vasculature and thereby augment the infiltration of CD8$^+$ T cells, promoting tumor rejection. Additionally, this group showed that ACT of eosinophils and T cells exerts changes in the TME vasculature and induces macrophage polarization toward an anti-inflammatory phenotype (Carretero et al., 2015). A more recent study by Zheng and colleagues (Zheng et al., 2020) showed that, upon ICB treatment in a mouse model of breast cancer, eosinophil infiltration in the TME increased. This was again associated with blood vessel normalization and increased T cell infiltration. The presence of eosinophils correlated with the positive outcome of the therapy in a pre-clinical model (Zheng et al., 2020).

Despite the above anti-tumorigenic evidence, eosinophils have also been described to exert pro-tumorigenic activities by establishing an immunosuppressive TME. In asthmatic patients, eosinophils are a major source of TGF-β and their granules contain VEGF (Horiuchi and Weller, 1997). Furthermore, eosinophil-derived IL-13 and CCL22 were shown to promote polarization of TAMs toward an immunosuppressive phenotype and Treg cell recruitment, respectively (Kratochvill et al., 2015; Zaynagetdinov et al., 2015).

Hypothetically, the controversial role of eosinophils in cancer may be explained by their metabolic plasticity, as it appears to be true for macrophages and neutrophils. However, more research is needed to unravel how metabolism in eosinophils changes under physiological conditions versus in the TME. Porter et al. (2018) recently compared the metabolic profile of circulating neutrophils and eosinophils obtained from healthy donors and activated *in vitro*. Eosinophils appeared to consume more oxygen than did neutrophils, as demonstrated by the eosinophils' increased basal rate of oxygen consumption rate (OCR), ATP-linked OCR, and maximal and spare respiratory capacity. The study shows that eosinophils are indeed able to use glycolysis and this shift can occur under hypoxic conditions

(Porter et al., 2018). Further insight is needed to establish a mechanistic view on the energetic pathways used by eosinophils and neutrophils in the tumor, in order to draw new therapeutic strategies.

DCs

DCs are professional APCs that prime T cells to mount adaptive immune responses. DCs recognize pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) via pattern recognition receptors (PRRs). PRR engagement by external stimuli spurs DC activation and maturation and initiates signaling for increased expression of co-stimulatory molecules (e.g., CD40 and CD86) and cytokines (e.g., IL-12 and TNF-α). Major histocompatibility complex (MHC) molecules are induced, facilitating antigen presentation. DCs load antigenic peptides onto MHC class I or II and migrate to the local LN, where they prime $CD4^+$ or $CD8^+$ T cells (Pearce and Everts, 2015).

It should be noted that most studies aimed at deciphering the metabolic needs of DCs have been performed *in vitro* using murine bone-marrow-derived DCs (BMDCs) subjected to exogenous PRR stimulation. Whether these results translate accurately to the TME context requires more investigation, but the insights gained have opened up new research perspectives (Giovanelli et al., 2019).

Glucose and Fatty Acids

Immature DCs rely on FAO to feed the ETC and OXPHOS to supply their energetic demands. This energetic status is sustained by PPARγ and PGC1α signaling cascades that fuel lipid metabolism and mitochondrial biogenesis, respectively. Early during tumor development, immature DCs phagocytose debris from apoptotic tumor cells. DAMPs in this debris engage the DC's PRRs to deliver signals that activate mTOR and Myc and induce a switch from FAO to glycolysis. The DCs increase their glucose uptake and lactate production, and glycolysis-derived pyruvate enters the mitochondria to fuel citrate production and FA synthesis. Newly formed lipids bolster the DC's endoplasmic reticulum (ER) and Golgi apparatus, supporting the increased demand for protein synthesis. Chemokine receptors, co-stimulatory molecules, cytokines, and elements of the antigen-presenting machinery are all expressed (Everts et al., 2014). Later during activation, the mature DCs commit exclusively to aerobic glycolysis with near complete loss of mitochondrial function. This engagement of Warburg metabolism depends on ETC inhibition by iNOS-derived NO (Krawczyk et al., 2010; Everts et al., 2012).

Given the importance of DCs to anti-tumor responses, this cell type is often subverted by the TME, resulting in the development of tumor-associated DCs with an immunosuppressive phenotype.

TME-Mediated Immunosuppression

Glucose deprivation in the TME decreases CCR7 expression in DCs and thus their homing to LN, reducing T cell activation (Guak et al., 2018). Low glucose and glutamine may interfere with protein glycosylation in a DC's ER, inducing the unfolded protein response (UPR), low mitochondrial function, and inhibition of DC activation (Song and Cubillos-Ruiz, 2019). The scarce availability of nutrients in the TME may promote tolerogenic DCs. In low nutrient availability, these APCs can inhibit mTOR signaling. This induces adenosine monophosphate kinase (AMPK) and PPARγ signaling, promoting mitochondrial respiration and biogenesis and oxidative metabolism (O'Neill and Pearce, 2016). In addition, Wnt/β-catenin signaling from cancer cells and consequent FAO engagement in tumor DCs have been shown to upregulate IDO in the latter. The resulting degradation of tryptophan and synthesis of kynurenine promote Treg cell development but Teff cell death (Zhao et al., 2018). Because tumor DCs express AHR, the released kynurenine sustains their IDO expression (Li et al., 2016). IDO production by TGF-β-stimulated DCs is also controlled by ARG1. ARG1 reduces the availability of arginine, which is needed for proper T cell function, and further promotes tryptophan metabolism (Mondanelli et al., 2017). CTLA4 expressed on Treg cells that interacts with CD80 on DCs drives IDO secretion in the DCs through the non-canonical NF-κB pathway (Grohmann et al., 2002).

Lipids and ER Stress

FAO metabolism in DCs is subverted in the TME. Lipid droplets accumulate in DCs due to either increased *de novo* FA synthesis or import via the scavenger receptor MSR1. ROS also accumulate in DCs due to the hypoxia of the TME and NOX activity induced by PRR engagement (Reczek and Chandel, 2017). These elevated ROS oxidize the plentiful lipids, leading to their excessive binding to heat shock protein 70 (Hsp70). This binding blocks the trafficking of MHC-peptide complexes to the DC membrane (Veglia et al., 2017), thereby reducing DC antigen-presenting capacity and thus T cell priming (Herber et al., 2010). In addition, lipid peroxidation induces the UPR and ER stress responses in DCs through serine/threonine-protein kinase/endoribonuclease (IRE1α) and x-box binding protein (XBP1) (Osorio et al., 2014; Iwakoshi et al., 2007). These responses hinder the transport of effector molecules and cytokines to the DC surface, again interfering with T cell priming. Lastly, both tumor cells and tumor DCs produce PGE_2, which reduces IL-12 production by DCs, thereby inhibiting Th1, $CD8^+$ T, and NK cell responses (Zelenay et al., 2015; Böttcher et al., 2018)

Several therapeutic approaches can target lipid metabolism in tumor DCs. Administration of 5-(tetradecycloxy)-2-furoic acid (TOFA)-1 to tumor-bearing mice attenuated lipid metabolism in tumor DCs and restored their ability to prime T cells (Herber et al., 2010). In a mouse melanoma model, inhibition of FAO with etomoxir synergized with PD-1 ICB to control tumor growth. Lastly, when etomoxir-treated BMDCs were used for ACT in mice, Treg cells and tumor burden were reduced (Zhao et al., 2018). Other pre-clinical evidence derived from *in vivo* ovarian cancer mouse models and *ex vivo* patient samples has shown that targeting lipogenesis and the ER stress response is effective in tumor control. Small interfering RNAs (siRNAs) against elements of the IRE1α-XBP1 signaling pathway can reduce lipid formation in tumor-infiltrating DCs, leading to a more robust Teff cell response and increased patient survival (Cubillos-Ruiz et al., 2015).

Hif1α and NO

In a hypoxic TME, DCs initiate anaerobic glycolysis and the consequent production of high levels of lactate have detrimental autocrine and paracrine effects. Hif1α induces DCs to express PD-L1 and $A_{2B}R$, leading to IL-10 and IDO production (Gottfried

et al., 2006; Noman et al., 2014; Yang et al., 2010). These immunosuppressive cytokines and metabolites are known to have a detrimental effect on the anti-tumor response. Inhibition of Hif1α signaling in BMDCs mediated by either genetic ablation or galactose treatment increases IL-12 and TNF-α production and boosts Teff cell activation and proliferation (Lawless et al., 2017).

DC production of NO also contributes to immunosuppression in the TME. In the synapse formed between DCs and T cells during antigen presentation, mitochondria in the latter are located close to the synapse, increasing their vulnerability to harmful effects of NO (Quintana et al., 2007; Pearce and Everts, 2015). As previously noted, NO can drive anaerobic glycolysis in DCs and respective tolerogenic function, more specifically in late stages of activation (Everts et al., 2012). From a therapy standpoint, given the plasticity of DCs, we hypothesize that a combinatorial approach targeting mTOR and iNOS should be considered. Inhibition of mTOR with rapamycin increases the lifespan and mitochondrial activity of lipopolysaccharides (LPS)-stimulated BMDCs *in vitro*. In a B16 melanoma model, ACT of rapamycin-treated DCs resulted in increased activation of $CD8^+$ T cells (Amiel et al., 2012, 2014).

Strikingly, ACT of DCs has fallen behind T cell ACT in terms of clinical application. Given the success of modulation of DC metabolism at the pre-clinical level, additional translational studies are warranted that aim to make DC ACT a viable anti-tumoral therapy (see review Perez and De Palma, 2019).

B Cells

B cells are an important component of the adaptive immune response but have been overlooked as components of immunotherapy. Once activated by antigen engagement of their B cell receptors (BCRs), B cells both stimulate T cells and differentiate into plasma cells that produce antibodies mediating a humoral response. However, although B cells have been detected in the TME during early tumor development, their function here is not clear (Largeot et al., 2019).

Breg Cells

Like activated T cells, activated B cells undergo metabolic reprogramming and increase their glucose uptake and AA consumption (Doughty et al., 2006; Franchina et al., 2018a). Thus, the nutrient-depleted TME might interfere with B cell activation. Some B cells in the TME acquire a regulatory phenotype (Breg cells) and suppress T cell responses, favoring tumor progression. Specifically, Breg cells secrete IL-10 and TGF-β, blocking $CD4^+$ T cell proliferation and inducing Foxp3 in Treg cells (Lindner et al., 2013). Breg cells have been documented in breast, ovarian, colorectal, cervical, and prostate carcinomas (Lindner et al., 2013). In acute myeloid leukemia (AML) patients, the presence of Breg cells predicts a poor prognosis and shorter survival (Lv et al., 2019). Little is known about the development and metabolism of Breg cells. Tumor cells may engage CD40L and thereby induce Breg cell differentiation via direct cell contact (Zhou et al., 2016). In addition, tumors secrete leukotriene B4, TNF-α, and other growth factors that can induce an immunosuppressive phenotype in B cells (Wejksza et al., 2013; Han et al., 2014; Schioppa et al., 2011). Recruitment of IL-21-producing T cells by the tumor may indirectly induce Breg cells (Lindner et al., 2013).

Hif1α

Hif1α in the hypoxic TME may modulate B cell metabolism (Largeot et al., 2019). Hif1α drives IL-10 expression by B cells so that strategies counteracting Hif1α signaling might render B cells less immunosuppressive (Meng et al., 2018). However, in a mouse pancreatic cancer model, Hif1α stabilization prevented B cells from infiltrating the tumor, slowing its development (Lee et al., 2016). Thus, depending on the cancer type, Hif1α might promote or inhibit tumor growth, complicating exploitation of Hif1α as a B-cell-based immunotherapy.

ACT and ICB

The metabolic rewiring of T cells has become a popular strategy for cancer immunotherapy, but B cells have been largely understudied in this context. Engagement of CD40 on activated B cells by CD40L induces additional co-stimulatory molecules and cytokines that activate cytotoxic T cell responses (Carpenter et al., 2009). ACT of B cells activated by agonist CD40 antibodies has shown promise in mouse models of melanoma and lymphoma (Largeot et al., 2019).

Inhibition of Breg cells through ICB is also under investigation as an anti-tumor strategy. Despite our limited knowledge of their metabolism, it has been hypothesized that metabolic intervention could repolarize Breg cells into anti-tumorigenic B cells. Leukotriene B4, which induces Breg cell differentiation, is derived from arachidonate 5-lipoxygenase (ALOX5) activity. Thus, ALOX5 might constitute a target for immunotherapy (Wejksza et al., 2013). IL-21 stimulation of B cells also induces a Breg cell phenotype as well as IDO expression (Lindner et al., 2013). Hypothetically, IDO inhibition might reduce B-cell-mediated immunosuppression.

It is clear that much more basic research is needed to unravel B-cell-specific metabolic requirements and effector functions in the TME context.

Conclusions

Growing evidence suggests that the metabolic requirements of immune cells in the TME greatly influence the success of anti-cancer ICB immunotherapy. Solid tumors remain the biggest challenge, with response rates still under 40% (Lim and June, 2017; Hargadon et al., 2018). Enhancing immune cell fitness in the TME by metabolic manipulation could potentially improve this rate and open the door to effective combination strategies (Figure 3). Radio- or chemotherapy induces tumor cell death, increasing the availability of nutrients in the TME. This replenishment of nutrients appears to be crucial for immune cell activation and function in the TME. This strategy can be further supported by inhibiting glycolysis in tumor cells through mTOR or Hif1a blockade. IDO inhibition may reduce tryptophan catabolism, increasing its availability and decreasing its immunosuppressive metabolite kynurenine.

It is evident that no systemic therapies, including metabolic modulators, will have a specific target, unless they are engineered for that exclusive purpose. As tumor and immune cell function rely on a series of similar pathways, targeting metabolism to prevent tumor growth can consequently impair immune cell function. For instance, inhibitors of the mTOR pathway, such as rapamycin, successfully interfere with proliferation, growth, and survival of cancer cells. Notably, this drug is

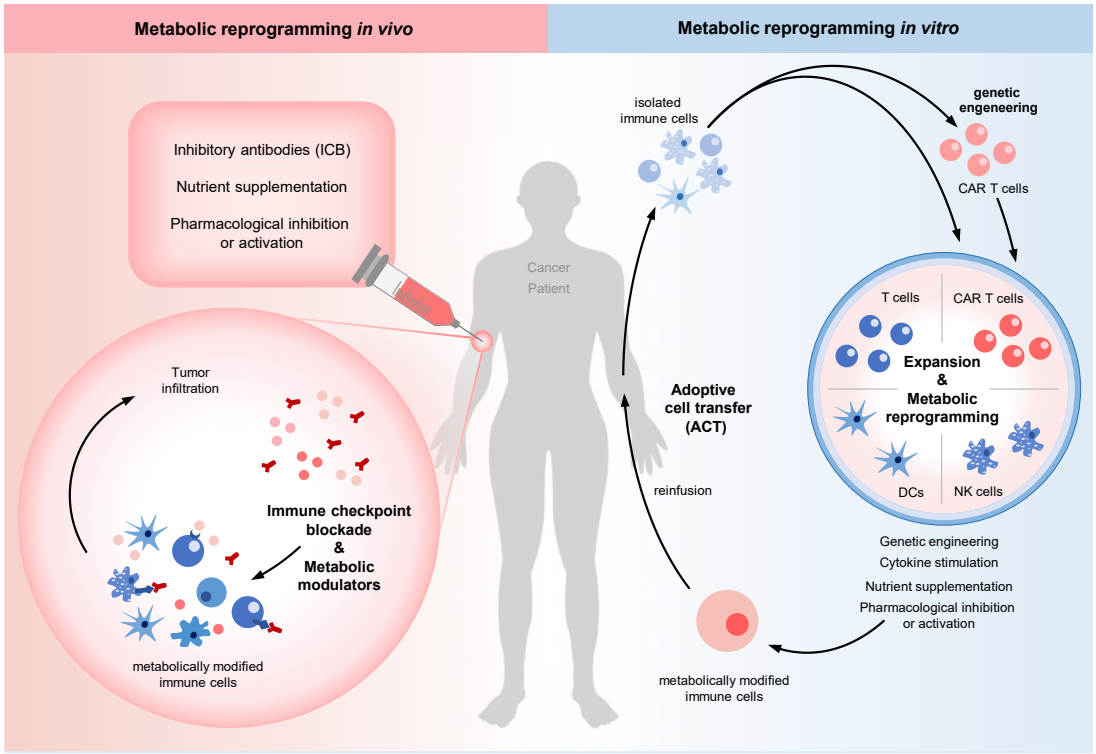


Figure 3. *In Vivo* and *In Vitro* Strategies for Metabolic Reprogramming of Immune Cells

Metabolic reprogramming of immune cells *in vivo* can be achieved by direct co-injection of a cancer patient with inhibitory antibodies mediating ICB plus metabolic modulators, such as pharmacological inhibitors or activators, or nutrient supplements. After treatment, the metabolically modified immune cells infiltrate the cancer and display high anti-tumor activity. For metabolic reprogramming of immune cells *in vitro*, immune cells, including T cells, NK cells, and DCs, are isolated from a cancer patient and expanded *in vitro*. These cells are treated with metabolic modulators, such as cytokines, inhibitors, activators, nutrients, or genetic modulators. In the case of CAR T therapy, the patient's isolated T cells are genetically modified to recognize a tumor antigen prior to metabolic reprogramming. Once metabolically altered, these immune cell populations with their improved anti-tumor activity are reinfused into the patient via adoptive cell transfer. The cells then infiltrate and attack the tumor. CAR T cells, chimeric antigen receptor T cells; ICB, immune checkpoint blockade.

used as an immunosuppressant to prevent graft rejection (McMahon et al., 2011). However, it was shown that inhibition of mTORC1 in tumors hinders MDSC accumulation, drives TAM anti-tumor function, augments DC activation, and induces $CD8^+$ T cell memory formation under specific conditions (Delgoffe et al., 2011; Guri et al., 2018). The dissection of the usage of energetic pathways by different players of the TME is crucial. Identifying how the distinct counterparts adapt differently to the inhibition of specific signaling would allow us a clear picture of metabolic plasticity in the TME. This knowledge in different types of cancers could be a valuable guide to design targeted immune metabolic modulators.

A recent paper from Leone et al. (2019) showed that interfering with glutaminolysis can target glutamine- and glucose-related pathways in cancer cells. This increases the nutrient and oxygen availability in the TME and sustains the function of their more metabolically flexible immune counterparts. The success of the use of glutamine antagonists in mouse models of cancer relied on the energetic plasticity of $CD8^+$ T cells. Contrary to the tested tumor cells, $CD8^+$ T cells were able to engage in acetate metabolism to generate ATP and maintain NADPH homeostasis. The increased metabolic fitness of the cytotoxic T cells led to an increased efficiency of the glutamine antagonists when combined with ICB therapy (Leone et al., 2019). Hypothetically, this could also increase NK-cell-mediated cytotoxicity, given that more glutamine in the TME would increase Myc-dependent NK cell activation, as proposed by O'Brien and Finlay (2019). The study of Leone et al. (2019) is in line with a recent publication from Qiu et al. (2019), describing that, in glucose-deprived environments, acetate can be used as an alternative substrate for histone acetylation. This favors chromatin accessibility in genes important for $CD8^+$ T cell effector function. Isolation of TILs from a glucose-deprived TME and supplementation of acetate *ex vivo* increased IFNγ production after stimulation compared to PBS-treated TILs. This underlines again that not only understanding nutrient competition but also metabolic tumor and immune cell plasticity is essential to develop future durable and effective immunotherapies (Qiu et al., 2019). Thus, the key might be to combine the systemic use of metabolic modulators with ICB to bring synergic benefits and allow an adjusted anti-tumor immune response.

Moreover, ACT constitutes a great strategy to overcome the need for systemic drug usage. Treatment of a single cell subtype *in vitro* and subsequent injection into the patient has proven to be

an efficient tool to improve anti-tumor response and improve patient prognosis. Early success has already been achieved, as with the 4-1BB co-stimulation approach in CAR T cells. Inclusion of 4-1BB in the architecture of a CAR T receptor increases the respiratory capacity, FAO, mitochondrial biogenesis, and *in vitro* persistence of CAR T cells (Kawalekar et al., 2016; ClinicalTrials.gov ID NCT02652455). ICB can also be combined with agonists of T cell co-stimulatory receptors. Agonistic 4-1BB signaling activates glucose and FA metabolism in $CD8^+$ Teff cells and enhances their proliferation (Choi et al., 2017). Nevertheless, the costs associated to this therapy are still high. One solution is to use nanoparticles that express molecules on their surface, which would engage target cells. Upon ligation, the content of these cells would be released closer to the specific cell and generate less systemic effects. This was recently described by Tang et al. (2018) by adoptively transferring T cells loaded with large amounts of IL-15 superagonist complex. These nanoparticles are only released upon encounter of the T cell with the antigen, allowing greater T cell expansion in the tumors (Tang et al., 2018). A similar approach can be used with metabolic modulators and short hairpin RNAs to specifically improve metabolic fitness of anti-tumor cells in the TME, as proposed by O'Sullivan et al. (2019).

The process of finding synergetic modulators can be accelerated by using drugs already in use for other pathologies, such as metformin or diclofenac. As has been detailed by Li et al. (2019), the results of several such *in vivo* models and phase I clinical trials have been encouraging (see review).

Moreover, there are other factors to consider. Emerging studies are attributing an immunomodulatory role to the gut microbiome, which likely influences immunotherapy outcomes. In melanoma patients, a "favorable" gut microbiome combined with PD-1 ICB resulted in enhanced anti-tumor responses associated with improved Teff cell function (Gopalakrishnan et al., 2018). Microbiota-derived short-chain FAs, such as butyrate, promote the formation of long-term $CD8^+$ memory T cells. These FAs decrease glycolysis and thus favor OXPHOS in these cells (Bachem et al., 2019). Thus, modulating immune cell metabolism by altering the gut microbiome or by administering microbiome-derived metabolites may be a novel adjunct to existing strategies.

Substantial literature indicates that there is an urgent need to identify the metabolic states and markers of immune cells in the TME so that clinicians can optimize immunotherapy for each patient. In our opinion, identifying combinations that target more than one cell type will be key to circumventing tumor-resistance mechanisms. Increasing our understanding of immunometabolism and how it is affected by the TME will open up innovative avenues for improving cancer immunotherapy.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

REFERENCES

Alves, N.L., Derks, I.A., Berk, E., Spijker, R., van Lier, R.A., and Eldering, E. (2006). The Noxa/Mcl-1 axis regulates susceptibility to apoptosis under glucose limitation in dividing T cells. Immunity *24*, 703–716.

Amiel, E., Everts, B., Freitas, T.C., King, I.L., Curtis, J.D., Pearce, E.L., and Pearce, E.J. (2012). Inhibition of mechanistic target of rapamycin promotes dendritic cell activation and enhances therapeutic autologous vaccination in mice. J. Immunol. *189*, 2151–2158.

Amiel, E., Everts, B., Fritz, D., Beauchamp, S., Ge, B., Pearce, E.L., and Pearce, E.J. (2014). Mechanistic target of rapamycin inhibition extends cellular lifespan in dendritic cells by preserving mitochondrial function. J. Immunol. *193*, 2821–2830.

André, P., Denis, C., Soulas, C., Bourbon-Caillet, C., Lopez, J., Arnoux, T., Bléry, M., Bonnafous, C., Gauthier, L., Morel, A., et al. (2018). Anti-NKG2A mAb is a checkpoint inhibitor that promotes anti-tumor immunity by unleashing both T and NK cells. Cell *175*, 1731–1743.e13.

Arts, R.J.W., Plantinga, T.S., Tuit, S., Ulas, T., Heinhuis, B., Tesselaar, M., Sloot, Y., Adema, G.J., Joosten, L.A.B., Smit, J.W.A., et al. (2016). Transcriptional and metabolic reprogramming induce an inflammatory phenotype in non-medullary thyroid carcinoma-induced macrophages. OncoImmunology *5*, e1229725.

Assmann, N., O'Brien, K.L., Donnelly, R.P., Dyck, L., Zaiatz-Bittencourt, V., Loftus, R.M., Heinrich, P., Oefner, P.J., Lynch, L., Gardiner, C.M., et al. (2017). Srebp-controlled glucose metabolism is essential for NK cell functional responses. Nat. Immunol. *18*, 1197–1206.

Bachem, A., Makhlouf, C., Binger, K.J., de Souza, D.P., Tull, D., Hochheiser, K., Whitney, P.G., Fernandez-Ruiz, D., Dähling, S., Kastenmüller, W., et al. (2019). Microbiota-derived short-chain fatty acids promote the memory potential of antigen-activated $CD8^+$ T cells. Immunity *51*, 285–297.e5.

Bailey, S.R., Nelson, M.H., Himes, R.A., Li, Z., Mehrotra, S., and Paulos, C.M. (2014). Th17 cells in cancer: the ultimate identity crisis. Front. Immunol. *5*, 276.

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

Beury, D.W., Parker, K.H., Nyandjo, M., Sinha, P., Carter, K.A., and Ostrand-Rosenberg, S. (2014). Cross-talk among myeloid-derived suppressor cells, macrophages, and tumor cells impacts the inflammatory milieu of solid tumors. J. Leukoc. Biol. *96*, 1109–1118.

Bohn, T., Rapp, S., Luther, N., Klein, M., Bruehl, T.-J., Kojima, N., Aranda Lopez, P., Hahlbrock, J., Muth, S., Endo, S., et al. (2018). Tumor immunoevasion via acidosis-dependent induction of regulatory tumor-associated macrophages. Nat. Immunol. *19*, 1319–1329.

Böttcher, J.P., Bonavita, E., Chakravarty, P., Blees, H., Cabeza-Cabrerizo, M., Sammicheli, S., Rogers, N.C., Sahai, E., Zelenay, S., and Reis E Sousa, C. (2018). NK Cells Stimulate Recruitment of cDC1 into the Tumor Microenvironment Promoting Cancer Immune Control. Cell *172*, 1022–1037.e14.

Brand, A., Singer, K., Koehl, G.E., Kolitzus, M., Schoenhammer, G., Thiel, A., Matos, C., Bruss, C., Klobuch, S., Peter, K., et al. (2016). LDHA-associated lactic acid production blunts tumor immunosurveillance by T and NK cells. Cell Metab. *24*, 657–671.

Capone, M., Giannarelli, D., Mallardo, D., Madonna, G., Festino, L., Grimaldi, A.M., Vanella, V., Simeone, E., Paone, M., Palmieri, G., et al. (2018). Baseline neutrophil-to-lymphocyte ratio (NLR) and derived NLR could predict overall survival in patients with advanced melanoma treated with nivolumab. J. Immunother. Cancer *6*, 74.

Carmona-Fontaine, C., Deforet, M., Akkari, L., Thompson, C.B., Joyce, J.A., and Xavier, J.B. (2017). Metabolic origins of spatial organization in the tumor microenvironment. Proc. Natl. Acad. Sci. USA *114*, 2934–2939.

Carpenter, E.L., Mick, R., Rüter, J., and Vonderheide, R.H. (2009). Activation of human B cells by the agonist CD40 antibody CP-870,893 and augmentation with simultaneous toll-like receptor 9 stimulation. J. Transl. Med. *7*, 93.

Carretero, R., Sektioglu, I.M., Garbi, N., Salgado, O.C., Beckhove, P., and Hämmerling, G.J. (2015). Eosinophils orchestrate cancer rejection by normalizing tumor vessels and enhancing infiltration of CD8(+) T cells. Nat. Immunol. *16*, 609–617.

Cham, C.M., Driessens, G., O'Keefe, J.P., and Gajewski, T.F. (2008). Glucose deprivation inhibits multiple key gene expression events and effector functions in CD8+ T cells. Eur. J. Immunol. *38*, 2438–2450.

Chambers, A.M., Wang, J., Lupo, K.B., Yu, H., Atallah Lanman, N.M., and Matosevic, S. (2018). Adenosinergic signaling alters natural killer cell functional responses. Front. Immunol. *9*, 2533.

Chandel, N.S., Maltepe, E., Goldwasser, E., Mathieu, C.E., Simon, M.C., and Schumacker, P.T. (1998). Mitochondrial reactive oxygen species trigger hypoxia-induced transcription. Proc. Natl. Acad. Sci. USA *95*, 11715–11720.

Chang, C.H., Qiu, J., O'Sullivan, D., Buck, M.D., Noguchi, T., Curtis, J.D., Chen, Q., Gindin, M., Gubin, M.M., van der Windt, G.J., et al. (2015). Metabolic competition in the tumor microenvironment is a driver of cancer progression. Cell *162*, 1229–1241.

Chiu, D.K.-C., Tse, A.P.-W., Xu, I.M.-J., Di Cui, J., Lai, R.K.-H., Li, L.L., Koh, H.-Y., Tsang, F.H.-C., Wei, L.L., Wong, C.-M., et al. (2017). Hypoxia inducible factor HIF-1 promotes myeloid-derived suppressor cells accumulation through ENTPD2/CD39L1 in hepatocellular carcinoma. Nat. Commun. *8*, 517.

Choi, B.K., Lee, D.Y., Lee, D.G., Kim, Y.H., Kim, S.H., Oh, H.S., Han, C., and Kwon, B.S. (2017). 4-1BB signaling activates glucose and fatty acid metabolism to enhance $CD8^+$ T cell proliferation. Cell. Mol. Immunol. *14*, 748–757.

Chowdhury, P.S., Chamoto, K., Kumar, A., and Honjo, T. (2018). PPAR-induced fatty acid oxidation in T cells increases the number of tumor-reactive $CD8^+$ T cells and facilitates anti-PD-1 therapy. Cancer Immunol. Res. *6*, 1375–1387.

Chun, E., Lavoie, S., Michaud, M., Gallini, C.A., Kim, J., Soucy, G., Odze, R., Glickman, J.N., and Garrett, W.S. (2015). CCL2 promotes colorectal carcinogenesis by enhancing polymorphonuclear myeloid-derived suppressor cell population and function. Cell Rep. *12*, 244–257.

Clambey, E.T., McNamee, E.N., Westrich, J.A., Glover, L.E., Campbell, E.L., Jedlicka, P., de Zoeten, E.F., Cambier, J.C., Stenmark, K.R., Colgan, S.P., and Eltzschig, H.K. (2012). Hypoxia-inducible factor-1 alpha-dependent induction of FoxP3 drives regulatory T-cell abundance and function during inflammatory hypoxia of the mucosa. Proc. Natl. Acad. Sci. USA *109*, E2784–E2793.

Coffelt, S.B., Wellenstein, M.D., and de Visser, K.E. (2016). Neutrophils in cancer: neutral no more. Nat. Rev. Cancer *16*, 431–446.

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. (2014). Functional polarization of tumour-associated macrophages by tumour-derived lactic acid. Nature *513*, 559–563.

Cong, J., Wang, X., Zheng, X., Wang, D., Fu, B., Sun, R., Tian, Z., and Wei, H. (2018). Dysfunction of natural killer cells by FBP1-induced inhibition of glycolysis during lung cancer progression. Cell Metab. *28*, 243–255.e5.

Corzo, C.A., Cotter, M.J., Cheng, P., Cheng, F., Kusmartsev, S., Sotomayor, E., Padhya, T., McCaffrey, T.V., McCaffrey, J.C., and Gabrilovich, D.I. (2009). Mechanism regulating reactive oxygen species in tumor-induced myeloid-derived suppressor cells. J. Immunol. *182*, 5693–5701.

Cubillos-Ruiz, J.R., Silberman, P.C., Rutkowski, M.R., Chopra, S., Perales-Puchalt, A., Song, M., Zhang, S., Bettigole, S.E., Gupta, D., Holcomb, K., et al. (2015). ER stress sensor XBP1 controls anti-tumor immunity by disrupting dendritic cell homeostasis. Cell *161*, 1527–1538.

Dang, E.V., Barbi, J., Yang, H.Y., Jinasena, D., Yu, H., Zheng, Y., Bordman, Z., Fu, J., Kim, Y., Yen, H.R., et al. (2011). Control of T(H)17/T(reg) balance by hypoxia-inducible factor 1. Cell *146*, 772–784.

Dao, T.M., and Matosevic, S. (2019). Immunometabolic responses of natural killer cells to inhibitory tumor microenvironment checkpoints. Immunometabolism *1*, e190003.

Delgoffe, G.M., Pollizzi, K.N., Waickman, A.T., Heikamp, E., Meyers, D.J., Horton, M.R., Xiao, B., Worley, P.F., and Powell, J.D. (2011). The kinase mTOR regulates the differentiation of helper T cells through the selective activation of signaling by mTORC1 and mTORC2. Nat. Immunol. *12*, 295–303.

Delgoffe, G.M., Kole, T.P., Zheng, Y., Zarek, P.E., Matthews, K.L., Xiao, B., Worley, P.F., Kozma, S.C., and Powell, J.D. (2009). The mTOR kinase differentially regulates effector and regulatory T cell lineage commitment. Immunity *30*, 832–844.

Delyon, J., Mateus, C., Lefeuvre, D., Lanoy, E., Zitvogel, L., Chaput, N., Roy, S., Eggermont, A.M., Routier, E., and Robert, C. (2013). Experience in daily practice with ipilimumab for the treatment of patients with metastatic melanoma: an early increase in lymphocyte and eosinophil counts is associated with improved survival. Ann. Oncol. *24*, 1697–1703.

Ding, X., Du, H., Yoder, M.C., and Yan, C. (2014). Critical role of the mTOR pathway in development and function of myeloid-derived suppressor cells in lal-/- mice. Am. J. Pathol. *184*, 397–408.

Divakaruni, A.S., Hsieh, W.Y., Minarrieta, L., Duong, T.N., Kim, K.K.O., Desousa, B.R., Andreyev, A.Y., Bowman, C.E., Caradonna, K., Dranka, B.P., et al. (2018). Etomoxir inhibits macrophage polarization by disrupting CoA homeostasis. Cell Metab. *28*, 490–503.e7.

Donnelly, R.P., Loftus, R.M., Keating, S.E., Liou, K.T., Biron, C.A., Gardiner, C.M., and Finlay, D.K. (2014). mTORC1-dependent metabolic reprogramming is a prerequisite for NK cell effector function. J. Immunol. *193*, 4477–4484.

Doughty, C.A., Bleiman, B.F., Wagner, D.J., Dufort, F.J., Mataraza, J.M., Roberts, M.F., and Chiles, T.C. (2006). Antigen receptor-mediated changes in glucose metabolism in B lymphocytes: role of phosphatidylinositol 3-kinase signaling in the glycolytic control of growth. Blood *107*, 4458–4465.

Everts, B., Amiel, E., van der Windt, G.J., Freitas, T.C., Chott, R., Yarasheski, K.E., Pearce, E.L., and Pearce, E.J. (2012). Commitment to glycolysis sustains survival of NO-producing inflammatory dendritic cells. Blood *120*, 1422–1431.

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. (2014). TLR-driven early glycolytic reprogramming via the kinases TBK1-IKKε supports the anabolic demands of dendritic cell activation. Nat. Immunol. *15*, 323–332.

Fares, C.M., Van Allen, E.M., Drake, C.G., Allison, J.P., and Hu-Lieskovan, S. (2019). Mechanisms of resistance to immune checkpoint blockade: why does checkpoint inhibitor immunotherapy not work for all patients? Am. Soc. Clin. Oncol. Educ. Book *39*, 147–164.

Field, C.S., Baixauli, F., Kyle, R.L., Puleston, D.J., Cameron, A.M., Sanin, D.E., Hippen, K.L., Loschi, M., Thangavelu, G., Corrado, M., et al. (2020). Mitochondrial integrity regulated by lipid metabolism is a cell-intrinsic checkpoint for Treg suppressive function. Cell Metab. *31*, 422–437.e5.

Franchina, D.G., Grusdat, M., and Brenner, D. (2018a). B-cell metabolic remodeling and cancer. Trends Cancer *4*, 138–150.

Franchina, D.G., He, F., and Brenner, D. (2018b). Survival of the fittest: cancer challenges T cell metabolism. Cancer Lett. *412*, 216–223.

Frauwirth, K.A., Riley, J.L., Harris, M.H., Parry, R.V., Rathmell, J.C., Plas, D.R., Elstrom, R.L., June, C.H., and Thompson, C.B. (2002). The CD28 signaling pathway regulates glucose metabolism. Immunity *16*, 769–777.

Frumento, G., Rotondo, R., Tonetti, M., Damonte, G., Benatti, U., and Ferrara, G.B. (2002). Tryptophan-derived catabolites are responsible for inhibition of T and natural killer cell proliferation induced by indoleamine 2,3-dioxygenase. J. Exp. Med. *196*, 459–468.

Gardiner, C.M. (2019). NK cell metabolism. J. Leukoc. Biol. *105*, 1235–1242.

Gauci, M.-L., Lanoy, E., Champiat, S., Caramella, C., Ammari, S., Aspeslagh, S., Varga, A., Baldini, C., Bahleda, R., Gazzah, A., et al. (2019). Long-term

survival in patients responding to anti-PD-1/PD-L1 therapy and disease outcome upon treatment discontinuation. Clin. Cancer Res. *25*, 946–956.

Gautier, E.L., Shay, T., Miller, J., Greter, M., Jakubzick, C., Ivanov, S., Helft, J., Chow, A., Elpek, K.G., Gordonov, S., et al.; Immunological Genome Consortium (2012). Gene-expression profiles and transcriptional regulatory pathways that underlie the identity and diversity of mouse tissue macrophages. Nat. Immunol. *13*, 1118–1128.

Geiger, R., Rieckmann, J.C., Wolf, T., Basso, C., Feng, Y., Fuhrer, T., Kogadeeva, M., Picotti, P., Meissner, F., Mann, M., et al. (2016). L-arginine modulates T cell metabolism and enhances survival and anti-tumor activity. Cell *167*, 829–842.e13.

Gentles, A.J., Newman, A.M., Liu, C.L., Bratman, S.V., Feng, W., Kim, D., Nair, V.S., Xu, Y., Khuong, A., Hoang, C.D., et al. (2015). The prognostic landscape of genes and infiltrating immune cells across human cancers. Nat. Med. *21*, 938–945.

Giovanelli, P., Sandoval, T.A., and Cubillos-Ruiz, J.R. (2019). Dendritic cell metabolism and function in tumors. Trends Immunol. *40*, 699–718.

Gopalakrishnan, V., Spencer, C.N., Nezi, L., Reuben, A., Andrews, M.C., Karpinets, T.V., Prieto, P.A., Vicente, D., Hoffman, K., Wei, S.C., et al. (2018). Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. Science *359*, 97–103.

Gottfried, E., Kunz-Schughart, L.A., Ebner, S., Mueller-Klieser, W., Hoves, S., Andreesen, R., Mackensen, A., and Kreutz, M. (2006). Tumor-derived lactic acid modulates dendritic cell activation and antigen expression. Blood *107*, 2013–2021.

Grohmann, U., Orabona, C., Fallarino, F., Vacca, C., Calcinaro, F., Falorni, A., Candeloro, P., Belladonna, M.L., Bianchi, R., Fioretti, M.C., and Puccetti, P. (2002). CTLA-4-Ig regulates tryptophan catabolism in vivo. Nat. Immunol. *3*, 1097–1101.

Groth, C., Hu, X., Weber, R., Fleming, V., Altevogt, P., Utikal, J., and Umansky, V. (2019). Immunosuppression mediated by myeloid-derived suppressor cells (MDSCs) during tumour progression. Br. J. Cancer *120*, 16–25.

Guak, H., Al Habyan, S., Ma, E.H., Aldossary, H., Al-Masri, M., Won, S.Y., Ying, T., Fixman, E.D., Jones, R.G., McCaffrey, L.M., and Krawczyk, C.M. (2018). Glycolytic metabolism is essential for CCR7 oligomerization and dendritic cell migration. Nat. Commun. *9*, 2463.

Guri, Y., Nordmann, T.M., and Roszik, J. (2018). mTOR at the transmitting and receiving ends in tumor immunity. Front. Immunol. *9*, 578.

Haas, R., Smith, J., Rocher-Ros, V., Nadkarni, S., Montero-Melendez, T., D'Acquisto, F., Bland, E.J., Bombardieri, M., Pitzalis, C., Perretti, M., et al. (2015). Lactate regulates metabolic and pro-inflammatory circuits in control of T cell migration and effector functions. PLoS Biol. *13*, e1002202.

Halestrap, A.P. (2012). The monocarboxylate transporter family–Structure and functional characterization. IUBMB Life *64*, 1–9.

Han, S., Feng, S., Ren, M., Ma, E., Wang, X., Xu, L., and Xu, M. (2014). Glioma cell-derived placental growth factor induces regulatory B cells. Int. J. Biochem. Cell Biol. *57*, 63–68.

Hanahan, D., and Weinberg, R.A. (2011). Hallmarks of cancer: the next generation. Cell *144*, 646–674.

Hargadon, K.M., Johnson, C.E., and Williams, C.J. (2018). Immune checkpoint blockade therapy for cancer: an overview of FDA-approved immune checkpoint inhibitors. Int. Immunopharmacol. *62*, 29–39.

Harmon, C., Robinson, M.W., Hand, F., Almuaili, D., Mentor, K., Houlihan, D.D., Hoti, E., Lynch, L., Geoghegan, J., and O'Farrelly, C. (2019). Lactate-mediated acidification of tumor microenvironment induces apoptosis of liver-resident NK cells in colorectal liver metastasis. Cancer Immunol. Res. *7*, 335–346.

Harris, I.S., Treloar, A.E., Inoue, S., Sasaki, M., Gorrini, C., Lee, K.C., Yung, K.Y., Brenner, D., Knobbe-Thomsen, C.B., Cox, M.A., et al. (2015). Glutathione and thioredoxin antioxidant pathways synergize to drive cancer initiation and progression. Cancer Cell *27*, 211–222.

Hartmann, J., Schüßler-Lenz, M., Bondanza, A., and Buchholz, C.J. (2017). Clinical development of CAR T cells-challenges and opportunities in translating innovative treatment concepts. EMBO Mol. Med. *9*, 1183–1197.

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. (2010). Lipid accumulation and dendritic cell dysfunction in cancer. Nat. Med. *16*, 880–886.

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. (2015). Phosphoenolpyruvate Is a Metabolic Checkpoint of Anti-tumor T Cell Responses. Cell *162*, 1217–1228.

Holmgaard, R.B., Zamarin, D., Li, Y., Gasmi, B., Munn, D.H., Allison, J.P., Merghoub, T., and Wolchok, J.D. (2015). Tumor-expressed IDO recruits and activates MDSCs in a Treg-dependent manner. Cell Rep. *13*, 412–424.

Horiuchi, T., and Weller, P.F. (1997). Expression of vascular endothelial growth factor by human eosinophils: upregulation by granulocyte macrophage colony-stimulating factor and interleukin-5. Am. J. Respir. Cell Mol. Biol. *17*, 70–77.

Hossain, F., Al-Khami, A.A., Wyczechowska, D., Hernandez, C., Zheng, L., Reiss, K., Valle, L.D., Trillo-Tinoco, J., Maj, T., Zou, W., et al. (2015). Inhibition of fatty acid oxidation modulates immunosuppressive functions of myeloid-derived suppressor cells and enhances cancer therapies. Cancer Immunol. Res. *3*, 1236–1247.

Hsu, B.E., Tabariès, S., Johnson, R.M., Andrzejewski, S., Senecal, J., Lehuédé, C., Annis, M.G., Ma, E.H., Völs, S., Ramsay, L., et al. (2019). Immature low-density neutrophils exhibit metabolic flexibility that facilitates breast cancer liver metastasis. Cell Rep. *27*, 3902–3915.e6.

Hu, W., Wang, G., Huang, D., Sui, M., and Xu, Y. (2019). Cancer immunotherapy based on natural killer cells: current progress and new opportunities. Front. Immunol. *10*, 1205.

Huang, S., Apasov, S., Koshiba, M., and Sitkovsky, M. (1997). Role of A2a extracellular adenosine receptor-mediated signaling in adenosine-mediated inhibition of T-cell activation and expansion. Blood *90*, 1600–1610.

Iwakoshi, N.N., Pypaert, M., and Glimcher, L.H. (2007). The transcription factor XBP-1 is essential for the development and survival of dendritic cells. J. Exp. Med. *204*, 2267–2275.

Jensen, H., Potempa, M., Gotthardt, D., and Lanier, L.L. (2017). 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. *199*, 1967–1972.

Kawalekar, O.U., O'Connor, R.S., Fraietta, J.A., Guo, L., McGettigan, S.E., Posey, A.D., Jr., Patel, P.R., Guedan, S., Scholler, J., Keith, B., et al. (2016). Distinct signaling of coreceptors regulates specific metabolism pathways and impacts memory development in CAR T cells. Immunity *44*, 380–390.

Keating, S.E., Zaiatz-Bittencourt, V., Loftus, R.M., Keane, C., Brennan, K., Finlay, D.K., and Gardiner, C.M. (2016). Metabolic reprogramming supports IFN-γ production by CD56bright NK cells. J. Immunol. *196*, 2552–2560.

Keppel, M.P., Saucier, N., Mah, A.Y., Vogel, T.P., and Cooper, M.A. (2015). Activation-specific metabolic requirements for NK cell IFN-γ production. J. Immunol. *194*, 1954–1962.

Kim, J., and DeBerardinis, R.J. (2019). Mechanisms and implications of metabolic heterogeneity in cancer. Cell Metab. *30*, 434–446.

Kim, K., Skora, A.D., Li, Z., Liu, Q., Tam, A.J., Blosser, R.L., Diaz, L.A., Jr., Papadopoulos, N., Kinzler, K.W., Vogelstein, B., and Zhou, S. (2014). Eradication of metastatic mouse cancers resistant to immune checkpoint blockade by suppression of myeloid-derived cells. Proc. Natl. Acad. Sci. USA *111*, 11774–11779.

Kim, S.H., Li, M., Trousil, S., Zhang, Y., Pasca di Magliano, M., Swanson, K.D., and Zheng, B. (2017). Phenformin inhibits myeloid-derived suppressor cells and enhances the anti-tumor activity of PD-1 blockade in melanoma. J. Invest. Dermatol. *137*, 1740–1748.

Klebanoff, C.A., Gattinoni, L., Palmer, D.C., Muranski, P., Ji, Y., Hinrichs, C.S., Borman, Z.A., Kerkar, S.P., Scott, C.D., Finkelstein, S.E., et al. (2011).

Determinants of successful CD8+ T-cell adoptive immunotherapy for large established tumors in mice. Clin. Cancer Res. *17*, 5343–5352.

Kratochvill, F., Neale, G., Haverkamp, J.M., Van de Velde, L.A., Smith, A.M., Kawauchi, D., McEvoy, J., Roussel, M.F., Dyer, M.A., Qualls, J.E., and Murray, P.J. (2015). TNF counterbalances the emergence of M2 tumor macrophages. Cell Rep. *12*, 1902–1914.

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., and Pearce, E.J. (2010). Toll-like receptor-induced changes in glycolytic metabolism regulate dendritic cell activation. Blood *115*, 4742–4749.

Kurniawan, H., Franchina, D.G., Guerra, L., Bonetti, L., -Baguet, L.S., Grusdat, M., Schlicker, L., Hunewald, O., Dostert, C., Merz, M.P., et al. (2020). Glutathione restricts serine metabolism to preserve regulatory T cell function. Cell Metab. *31*, 920–936.e7.

Kusmartsev, S., Eruslanov, E., Kübler, H., Tseng, T., Sakai, Y., Su, Z., Kaliberov, S., Heiser, A., Rosser, C., Dahm, P., et al. (2008). Oxidative stress regulates expression of VEGFR1 in myeloid cells: link to tumor-induced immune suppression in renal cell carcinoma. J. Immunol. *181*, 346–353.

Largeot, A., Pagano, G., Gonder, S., Moussay, E., and Paggetti, J. (2019). The B-side of cancer immunity: the underrated tune. Cells *8*, 449.

Lawless, S.J., Kedia-Mehta, N., Walls, J.F., McGarrigle, R., Convery, O., Sinclair, L.V., Navarro, M.N., Murray, J., and Finlay, D.K. (2017). Glucose represses dendritic cell-induced T cell responses. Nat. Commun. *8*, 15620.

Lechner, M.G., Liebertz, D.J., and Epstein, A.L. (2010). Characterization of cytokine-induced myeloid-derived suppressor cells from normal human peripheral blood mononuclear cells. J. Immunol. *185*, 2273–2284.

Lecot, P., Sarabi, M., Pereira Abrantes, M., Mussard, J., Koenderman, L., Caux, C., Bendriss-Vermare, N., and Michallet, M.-C. (2019). Neutrophil heterogeneity in cancer: from biology to therapies. Front. Immunol. *10*, 2155.

Lee, K.E., Spata, M., Bayne, L.J., Buza, E.L., Durham, A.C., Allman, D., Vonderheide, R.H., and Simon, M.C. (2016). Hif1a deletion reveals pro-neoplastic function of B cells in pancreatic neoplasia. Cancer Discov. *6*, 256–269.

Leone, R.D., Zhao, L., Englert, J.M., Sun, I.-M., Oh, M.-H., Sun, I.-H., Arwood, M.L., Bettencourt, I.A., Patel, C.H., Wen, J., et al. (2019). Glutamine blockade induces divergent metabolic programs to overcome tumor immune evasion. Science *366*, 1013–1021.

Li, Q., Harden, J.L., Anderson, C.D., and Egilmez, N.K. (2016). Tolerogenic phenotype of IFN-γ-induced IDO^+ dendritic cells is maintained via an autocrine IDO-kynurenine/AhR-IDO loop. J. Immunol. *197*, 962–970.

Li, X., Wenes, M., Romero, P., Huang, S.C., Fendt, S.M., and Ho, P.C. (2019). Navigating metabolic pathways to enhance antitumour immunity and immunotherapy. Nat. Rev. Clin. Oncol. *16*, 425–441.

Lim, W.A., and June, C.H. (2017). The principles of engineering immune cells to treat cancer. Cell *168*, 724–740.

Lindner, S., Dahlke, K., Sontheimer, K., Hagn, M., Kaltenmeier, C., Barth, T.F., Beyer, T., Reister, F., Fabricius, D., Lotfi, R., et al. (2013). Interleukin 21-induced granzyme B-expressing B cells infiltrate tumors and regulate T cells. Cancer Res. *73*, 2468–2479.

Liu, H., Shen, Z., Wang, Z., Wang, X., Zhang, H., Qin, J., Qin, X., Xu, J., and Sun, Y. (2016). Increased expression of IDO associates with poor postoperative clinical outcome of patients with gastric adenocarcinoma. Sci. Rep. *6*, 21319.

Liu, P.S., Wang, H., Li, X., Chao, T., Teav, T., Christen, S., Di Conza, G., Cheng, W.C., Chou, C.H., Vavakova, M., et al. (2017). α-ketoglutarate orchestrates macrophage activation through metabolic and epigenetic reprogramming. Nat. Immunol. *18*, 985–994.

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. (2018). Amino acid-dependent cMyc expression is essential for NK cell metabolic and functional responses in mice. Nat. Commun. *9*, 2341.

Lv, Y., Wang, H., and Liu, Z. (2019). The role of regulatory B cells in patients with acute myeloid leukemia. Med. Sci. Monit. *25*, 3026–3031.

Macintyre, A.N., Gerriets, V.A., Nichols, A.G., Michalek, R.D., Rudolph, M.C., Deoliveira, D., Anderson, S.M., Abel, E.D., Chen, B.J., Hale, L.P., and Rathmell, J.C. (2014). The glucose transporter Glut1 is selectively essential for CD4 T cell activation and effector function. Cell Metab. *20*, 61–72.

MacMicking, J., Xie, Q.W., and Nathan, C. (1997). Nitric oxide and macrophage function. Annu. Rev. Immunol. *15*, 323–350.

Maj, T., Wang, W., Crespo, J., Zhang, H., Wang, W., Wei, S., Zhao, L., Vatan, L., Shao, I., Szeliga, W., et al. (2017). Oxidative stress controls regulatory T cell apoptosis and suppressor activity and PD-L1-blockade resistance in tumor. Nat. Immunol. *18*, 1332–1341.

Mak, T.W., Grusdat, M., Duncan, G.S., Dostert, C., Nonnenmacher, Y., Cox, M., Binsfeld, C., Hao, Z., Brüstle, A., Itsumi, M., et al. (2017). Glutathione primes T cell metabolism for inflammation. Immunity *46*, 675–689.

Marçais, A., Cherfils-Vicini, J., Viant, C., Degouve, S., Viel, S., Fenis, A., Rabilloud, J., Mayol, K., Tavares, A., Bienvenu, J., et al. (2014). The metabolic checkpoint kinase mTOR is essential for IL-15 signaling during the development and activation of NK cells. Nat. Immunol. *15*, 749–757.

McMahon, G., Weir, M.R., Li, X.C., and Mandelbrot, D.A. (2011). The evolving role of mTOR inhibition in transplantation tolerance. J. Am. Soc. Nephrol. *22*, 408–415.

Meng, X., Grötsch, B., Luo, Y., Knaup, K.X., Wiesener, M.S., Chen, X.X., Jantsch, J., Fillatreau, S., Schett, G., and Bozec, A. (2018). Hypoxia-inducible factor-1α is a critical transcription factor for IL-10-producing B cells in autoimmune disease. Nat. Commun. *9*, 251.

Mezrich, J.D., Fechner, J.H., Zhang, X., Johnson, B.P., Burlingham, W.J., and Bradfield, C.A. (2010). An interaction between kynurenine and the aryl hydrocarbon receptor can generate regulatory T cells. J. Immunol. *185*, 3190–3198.

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

Michelet, X., Dyck, L., Hogan, A., Loftus, R.M., Duquette, D., Wei, K., Beyaz, S., Tavakkoli, A., Foley, C., Donnelly, R., et al. (2018). Metabolic reprogramming of natural killer cells in obesity limits antitumor responses. Nat. Immunol. *19*, 1330–1340.

Miller, J.S., and Lanier, L.L. (2019). Natural killer cells in cancer immunotherapy. Ann. Rev. Cancer Biol. *3*, 77–103.

Miller, A., Nagy, C., Knapp, B., Laengle, J., Ponweiser, E., Groeger, M., Starkl, P., Bergmann, M., Wagner, O., and Haschemi, A. (2017). Exploring metabolic configurations of single cells within complex tissue microenvironments. Cell Metab. *26*, 788–800.e6.

Mills, E.L., Kelly, B., Logan, A., Costa, A.S.H., Varma, M., Bryant, C.E., Tourlomousis, P., Däbritz, J.H.M., Gottlieb, E., Latorre, I., et al. (2016). Succinate dehydrogenase supports metabolic repurposing of mitochondria to drive inflammatory macrophages. Cell *167*, 457–470.e13.

Mondanelli, G., Bianchi, R., Pallotta, M.T., Orabona, C., Albini, E., Iacono, A., Belladonna, M.L., Vacca, C., Fallarino, F., Macchiarulo, A., et al. (2017). A relay pathway between arginine and tryptophan metabolism confers immunosuppressive properties on dendritic cells. Immunity *46*, 233–244.

Morais, R., Zinkewich-Péotti, K., Parent, M., Wang, H., Babai, F., and Zollinger, M. (1994). Tumor-forming ability in athymic nude mice of human cell lines devoid of mitochondrial DNA. Cancer Res. *54*, 3889–3896.

Munn, D.H., Sharma, M.D., Baban, B., Harding, H.P., Zhang, Y., Ron, D., and Mellor, A.L. (2005). GCN2 kinase in T cells mediates proliferative arrest and anergy induction in response to indoleamine 2,3-dioxygenase. Immunity *22*, 633–642.

Nakaya, M., Xiao, Y., Zhou, X., Chang, J.H., Chang, M., Cheng, X., Blonska, M., Lin, X., and Sun, S.C. (2014). Inflammatory T cell responses rely on amino acid transporter ASCT2 facilitation of glutamine uptake and mTORC1 kinase activation. Immunity *40*, 692–705.

Ni, J., Miller, M., Stojanovic, A., Garbi, N., and Cerwenka, A. (2012). Sustained effector function of IL-12/15/18-preactivated NK cells against established tumors. J. Exp. Med. *209*, 2351–2365.

Noman, M.Z., Desantis, G., Janji, B., Hasmim, M., Karray, S., Dessen, P., Bronte, V., and Chouaib, S. (2014). PD-L1 is a novel direct target of HIF-1α, and its blockade under hypoxia enhanced MDSC-mediated T cell activation. J. Exp. Med. *211*, 781–790.

O'Brien, K.L., and Finlay, D.K. (2019). Immunometabolism and natural killer cell responses. Nat. Rev. Immunol. *19*, 282–290.

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

O'Sullivan, D., Sanin, D.E., Pearce, E.J., and Pearce, E.L. (2019). Metabolic interventions in the immune response to cancer. Nat. Rev. Immunol. *19*, 324–335.

Ohl, K., Fragoulis, A., Klemm, P., Baumeister, J., Klock, W., Verjans, E., Böll, S., Möllmann, J., Lehrke, M., Costa, I., et al. (2018). Nrf2 is a central regulator of metabolic reprogramming of myeloid-derived suppressor cells in steady state and sepsis. Front. Immunol. *9*, 1552.

Ohta, A., Kini, R., Ohta, A., Subramanian, M., Madasu, M., and Sitkovsky, M. (2012). The development and immunosuppressive functions of CD4(+) CD25(+) FoxP3(+) regulatory T cells are under influence of the adenosine-A2A adenosine receptor pathway. Front. Immunol. *3*, 190.

Opitz, C.A., Litzenburger, U.M., Sahm, F., Ott, M., Tritschler, I., Trump, S., Schumacher, T., Jestaedt, L., Schrenk, D., Weller, M., et al. (2011). An endogenous tumour-promoting ligand of the human aryl hydrocarbon receptor. Nature *478*, 197–203.

Osorio, F., Tavernier, S.J., Hoffmann, E., Saeys, Y., Martens, L., Vetters, J., Delrue, I., De Rycke, R., Parthoens, E., Pouliot, P., et al. (2014). The unfolded-protein-response sensor IRE-1α regulates the function of CD8α$^+$ dendritic cells. Nat. Immunol. *15*, 248–257.

Parameswaran, R., Ramakrishnan, P., Moreton, S.A., Xia, Z., Hou, Y., Lee, D.A., Gupta, K., deLima, M., Beck, R.C., and Wald, D.N. (2016). Repression of GSK3 restores NK cell cytotoxicity in AML patients. Nat. Commun. *7*, 11154.

Park, J., Lee, S.E., Hur, J., Hong, E.B., Choi, J.-I., Yang, J.-M., Kim, J.-Y., Kim, Y.-C., Cho, H.-J., Peters, J.M., et al. (2015). M-CSF from cancer cells induces fatty acid synthase and PPARβ/δ activation in tumor myeloid cells, leading to tumor progression. Cell Rep. *10*, 1614–1625.

Pathria, P., Louis, T.L., and Varner, J.A. (2019). Targeting Tumor-Associated Macrophages in Cancer. Trends Immunol. *40*, 310–327.

Pavlova, N.N., and Thompson, C.B. (2016). The emerging hallmarks of cancer metabolism. Cell Metab. *23*, 27–47.

Pearce, E.J., and Everts, B. (2015). Dendritic cell metabolism. Nat. Rev. Immunol. *15*, 18–29.

Pearce, E.L., Walsh, M.C., Cejas, P.J., Harms, G.M., Shen, H., Wang, L.S., Jones, R.G., and Choi, Y. (2009). Enhancing CD8 T-cell memory by modulating fatty acid metabolism. Nature *460*, 103–107.

Perez, C.R., and De Palma, M. (2019). Engineering dendritic cell vaccines to improve cancer immunotherapy. Nat. Commun. *10*, 5408.

Pilipow, K., Scamardella, E., Puccio, S., Gautam, S., De Paoli, F., Mazza, E.M., De Simone, G., Polletti, S., Buccilli, M., Zanon, V., et al. (2018). Antioxidant metabolism regulates CD8+ T memory stem cell formation and antitumor immunity. JCI Insight *3*, e122299.

Pilon-Thomas, S., Kodumudi, K.N., El-Kenawi, A.E., Russell, S., Weber, A.M., Luddy, K., Damaghi, M., Wojtkowiak, J.W., Mulé, J.J., Ibrahim-Hashim, A., and Gillies, R.J. (2016). Neutralization of tumor acidity improves antitumor responses to immunotherapy. Cancer Res. *76*, 1381–1390.

Porter, L., Toepfner, N., Bashant, K.R., Guck, J., Ashcroft, M., Farahi, N., and Chilvers, E.R. (2018). Metabolic profiling of human eosinophils. Front. Immunol. *9*, 1404.

Pötzl, J., Roser, D., Bankel, L., Hömberg, N., Geishauser, A., Brenner, C.D., Weigand, M., Röcken, M., and Mocikat, R. (2017). Reversal of tumor acidosis by systemic buffering reactivates NK cells to express IFN-γ and induces NK cell-dependent lymphoma control without other immunotherapies. Int. J. Cancer *140*, 2125–2133.

Qiu, J., Villa, M., Sanin, D.E., Buck, M.D., O'Sullivan, D., Ching, R., Matsushita, M., Grzes, K.M., Winkler, F., Chang, C.H., et al. (2019). Acetate promotes T cell effector function during glucose restriction. Cell Rep. *27*, 2063–2074.e5.

Quintana, A., Schwindling, C., Wenning, A.S., Becherer, U., Rettig, J., Schwarz, E.C., and Hoth, M. (2007). T cell activation requires mitochondrial translocation to the immunological synapse. Proc. Natl. Acad. Sci. USA *104*, 14418–14423.

Raud, B., Roy, D.G., Divakaruni, A.S., Tarasenko, T.N., Franke, R., Ma, E.H., Samborska, B., Hsieh, W.Y., Wong, A.H., Stüve, P., et al. (2018). Etomoxir actions on regulatory and memory T cells are independent of Cpt1a-mediated fatty acid oxidation. Cell Metab. *28*, 504–515.e7.

Reczek, C.R., and Chandel, N.S. (2017). The two faces of reactive oxygen species in cancer. Ann. Rev. Cancer Biol. *1*, 79–98.

Reichman, H., Karo-Atar, D., and Munitz, A. (2016). Emerging roles for eosinophils in the tumor microenvironment. Trends Cancer *2*, 664–675.

Renner, K., Bruss, C., Schnell, A., Koehl, G., Becker, H.M., Fante, M., Menevse, A.N., Kauer, N., Blazquez, R., Hacker, L., et al. (2019). Restricting glycolysis preserves T cell effector functions and augments checkpoint therapy. Cell Rep. *29*, 135–150.e9.

Rice, C.M., Davies, L.C., Subleski, J.J., Maio, N., Gonzalez-Cotto, M., Andrews, C., Patel, N.L., Palmieri, E.M., Weiss, J.M., Lee, J.-M., et al. (2018). Tumour-elicited neutrophils engage mitochondrial metabolism to circumvent nutrient limitations and maintain immune suppression. Nat. Commun. *9*, 5099.

Rodriguez, P.C., Quiceno, D.G., Zabaleta, J., Ortiz, B., Zea, A.H., Piazuelo, M.B., Delgado, A., Correa, P., Brayer, J., Sotomayor, E.M., et al. (2004). Arginase I production in the tumor microenvironment by mature myeloid cells inhibits T-cell receptor expression and antigen-specific T-cell responses. Cancer Res. *64*, 5839–5849.

Rodriguez, P.C., Quiceno, D.G., and Ochoa, A.C. (2007). L-arginine availability regulates T-lymphocyte cell-cycle progression. Blood *109*, 1568–1573.

Rosenberg, S.A., Restifo, N.P., Yang, J.C., Morgan, R.A., and Dudley, M.E. (2008). Adoptive cell transfer: a clinical path to effective cancer immunotherapy. Nat. Rev. Cancer *8*, 299–308.

Schadendorf, D., Hodi, F.S., Robert, C., Weber, J.S., Margolin, K., Hamid, O., Patt, D., Chen, T.T., Berman, D.M., and Wolchok, J.D. (2015). Pooled analysis of long-term survival data from phase II and phase III trials of ipilimumab in unresectable or metastatic melanoma. J. Clin. Oncol. *33*, 1889–1894.

Scharping, N.E., Menk, A.V., Moreci, R.S., Whetstone, R.D., Dadey, R.E., Watkins, S.C., Ferris, R.L., and Delgoffe, G.M. (2016). The tumor microenvironment represses T cell mitochondrial biogenesis to drive intratumoral T cell metabolic insufficiency and dysfunction. Immunity *45*, 374–388.

Scharping, N.E., Menk, A.V., Whetstone, R.D., Zeng, X., and Delgoffe, G.M. (2017). Efficacy of PD-1 blockade is potentiated by metformin-induced reduction of tumor hypoxia. Cancer Immunol. Res. *5*, 9–16.

Schindler, K., Harmankaya, K., Kuk, D., Mangana, J., Michielin, O., Hoeller, C., Dummer, R., Pehamberger, H., Wolchok, J.D., and Postow, M.A. (2014). Correlation of absolute and relative eosinophil counts with immune-related adverse events in melanoma patients treated with ipilimumab. J. Clin. Oncol. *32*, 9096.

Schioppa, T., Moore, R., Thompson, R.G., Rosser, E.C., Kulbe, H., Nedospasov, S., Mauri, C., Coussens, L.M., and Balkwill, F.R. (2011). B regulatory cells and the tumor-promoting actions of TNF-α during squamous carcinogenesis. Proc. Natl. Acad. Sci. USA *108*, 10662–10667.

Schlecker, E., Stojanovic, A., Eisen, C., Quack, C., Falk, C.S., Umansky, V., and Cerwenka, A. (2012). Tumor-infiltrating monocytic myeloid-derived suppressor cells mediate CCR5-dependent recruitment of regulatory T cells favoring tumor growth. J. Immunol. *189*, 5602–5611.

Sena, L.A., Li, S., Jairaman, A., Prakriya, M., Ezponda, T., Hildeman, D.A., Wang, C.R., Schumacker, P.T., Licht, J.D., Perlman, H., et al. (2013). Mitochondria are required for antigen-specific T cell activation through reactive oxygen species signaling. Immunity *38*, 225–236.

Sharma, S., Yang, S.C., Zhu, L., Reckamp, K., Gardner, B., Baratelli, F., Huang, M., Batra, R.K., and Dubinett, S.M. (2005). Tumor cyclooxygenase-

2/prostaglandin E2-dependent promotion of FOXP3 expression and CD4+ CD25+ T regulatory cell activities in lung cancer. Cancer Res. *65*, 5211–5220.

Sharma, M.D., Hou, D.Y., Liu, Y., Koni, P.A., Metz, R., Chandler, P., Mellor, A.L., He, Y., and Munn, D.H. (2009). Indoleamine 2,3-dioxygenase controls conversion of Foxp3+ Tregs to TH17-like cells in tumor-draining lymph nodes. Blood *113*, 6102–6111.

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

Shim, H., Dolde, C., Lewis, B.C., Wu, C.-S., Dang, G., Jungmann, R.A., Dalla-Favera, R., and Dang, C.V. (1997). c-Myc transactivation of LDH-A: implications for tumor metabolism and growth. Proc. Natl. Acad. Sci. USA *94*, 6658–6663.

Sica, A., Strauss, L., Consonni, F.M., Travelli, C., Genazzani, A., and Porta, C. (2017). Metabolic regulation of suppressive myeloid cells in cancer. Cytokine Growth Factor Rev. *35*, 27–35.

Sinclair, L.V., Rolf, J., Emslie, E., Shi, Y.B., Taylor, P.M., and Cantrell, D.A. (2013). Control of amino-acid transport by antigen receptors coordinates the metabolic reprogramming essential for T cell differentiation. Nat. Immunol. *14*, 500–508.

Siska, P.J., Beckermann, K.E., Mason, F.M., Andrejeva, G., Greenplate, A.R., Sendor, A.B., Chiang, Y.J., Corona, A.L., Gemta, L.F., Vincent, B.G., et al. (2017). Mitochondrial dysregulation and glycolytic insufficiency functionally impair CD8 T cells infiltrating human renal cell carcinoma. JCI Insight *2*, e93411.

Snijdewint, F.G., Kaliński, P., Wierenga, E.A., Bos, J.D., and Kapsenberg, M.L. (1993). Prostaglandin E2 differentially modulates cytokine secretion profiles of human T helper lymphocytes. J. Immunol. *150*, 5321–5329.

Song, M., and Cubillos-Ruiz, J.R. (2019). Endoplasmic reticulum stress responses in intratumoral immune cells: implications for cancer immunotherapy. Trends Immunol. *40*, 128–141.

Sonveaux, P., Copetti, T., De Saedeleer, C.J., Végran, F., Verrax, J., Kennedy, K.M., Moon, E.J., Dhup, S., Danhier, P., Frérart, F., et al. (2012). Targeting the lactate transporter MCT1 in endothelial cells inhibits lactate-induced HIF-1 activation and tumor angiogenesis. PLoS ONE *7*, e33418.

Stiff, A., Trikha, P., Mundy-Bosse, B., McMichael, E., Mace, T.A., Benner, B., Kendra, K., Campbell, A., Gautam, S., Abood, D., et al. (2018). Nitric oxide production by myeloid-derived suppressor cells plays a role in impairing Fc receptor-mediated natural killer cell function. Clin. Cancer Res. *24*, 1891–1904.

Sukumar, M., Liu, J., Ji, Y., Subramanian, M., Crompton, J.G., Yu, Z., Roychoudhuri, R., Palmer, D.C., Muranski, P., Karoly, E.D., et al. (2013). Inhibiting glycolytic metabolism enhances CD8+ T cell memory and antitumor function. J. Clin. Invest. *123*, 4479–4488.

Sun, C., Xu, J., Huang, Q., Huang, M., Wen, H., Zhang, C., Wang, J., Song, J., Zheng, M., Sun, H., et al. (2016). High NKG2A expression contributes to NK cell exhaustion and predicts a poor prognosis of patients with liver cancer. OncoImmunology *6*, e1264562.

Tan, A.S., Baty, J.W., Dong, L.F., Bezawork-Geleta, A., Endaya, B., Goodwin, J., Bajzikova, M., Kovarova, J., Peterka, M., Yan, B., et al. (2015). Mitochondrial genome acquisition restores respiratory function and tumorigenic potential of cancer cells without mitochondrial DNA. Cell Metab. *21*, 81–94.

Tanaka, A., and Sakaguchi, S. (2017). Regulatory T cells in cancer immunotherapy. Cell Res. *27*, 109–118.

Tang, L., Zheng, Y., Melo, M.B., Mabardi, L., Castaño, A.P., Xie, Y.-Q., Li, N., Kudchodkar, S.B., Wong, H.C., Jeng, E.K., et al. (2018). Enhancing T cell therapy through TCR-signaling-responsive nanoparticle drug delivery. Nat. Biotechnol. *36*, 707–716.

Templeton, A.J., McNamara, M.G., Šeruga, B., Vera-Badillo, F.E., Aneja, P., Ocaña, A., Leibowitz-Amit, R., Sonpavde, G., Knox, J.J., Tran, B., et al. (2014). Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. J. Natl. Cancer Inst. *106*, dju124.

Terrén, I., Orrantia, A., Vitallé, J., Zenarruzabeitia, O., and Borrego, F. (2019). NK cell metabolism and tumor microenvironment. Front. Immunol. *10*, 2278.

Thommen, D.S., Koelzer, V.H., Herzig, P., Roller, A., Trefny, M., Dimeloe, S., Kiialainen, A., Hanhart, J., Schill, C., Hess, C., et al. (2018). A transcriptionally and functionally distinct PD-1^{+} CD8^{+} T cell pool with predictive potential in non-small-cell lung cancer treated with PD-1 blockade. Nat. Med. *24*, 994–1004.

Triplett, T.A., Garrison, K.C., Marshall, N., Donkor, M., Blazeck, J., Lamb, C., Qerqez, A., Dekker, J.D., Tanno, Y., Lu, W.C., et al. (2018). Reversal of indoleamine 2,3-dioxygenase-mediated cancer immune suppression by systemic kynurenine depletion with a therapeutic enzyme. Nat. Biotechnol. *36*, 758–764.

van der Windt, G.J., O'Sullivan, D., Everts, B., Huang, S.C., Buck, M.D., Curtis, J.D., Chang, C.H., Smith, A.M., Ai, T., Faubert, B., et al. (2013). CD8 memory T cells have a bioenergetic advantage that underlies their rapid recall ability. Proc. Natl. Acad. Sci. USA *110*, 14336–14341.

Vats, D., Mukundan, L., Odegaard, J.I., Zhang, L., Smith, K.L., Morel, C.R., Wagner, R.A., Greaves, D.R., Murray, P.J., and Chawla, A. (2006). Oxidative metabolism and PGC-1beta attenuate macrophage-mediated inflammation. Cell Metab. *4*, 13–24.

Veglia, F., Tyurin, V.A., Mohammadyani, D., Blasi, M., Duperret, E.K., Donthireddy, L., Hashimoto, A., Kapralov, A., Amoscato, A., Angelini, R., et al. (2017). Lipid bodies containing oxidatively truncated lipids block antigen cross-presentation by dendritic cells in cancer. Nat. Commun. *8*, 2122.

Végran, F., Boidot, R., Michiels, C., Sonveaux, P., and Feron, O. (2011). Lactate influx through the endothelial cell monocarboxylate transporter MCT1 supports an NF-κB/IL-8 pathway that drives tumor angiogenesis. Cancer Res. *71*, 2550–2560.

Velásquez, S.Y., Killian, D., Schulte, J., Sticht, C., Thiel, M., and Lindner, H.A. (2016). Short term hypoxia synergizes with interleukin 15 priming in driving glycolytic gene transcription and supports human natural killer cell activities. J. Biol. Chem. *291*, 12960–12977.

Viel, S., Marçais, A., Guimaraes, F.S., Loftus, R., Rabilloud, J., Grau, M., Degouve, S., Djebali, S., Sanlaville, A., Charrier, E., et al. (2016). TGF-β inhibits the activation and functions of NK cells by repressing the mTOR pathway. Sci. Signal. *9*, ra19.

Vigano, S., Alatzoglou, D., Irving, M., Ménétrier-Caux, C., Caux, C., Romero, P., and Coukos, G. (2019). Targeting adenosine in cancer immunotherapy to enhance T-cell function. Front. Immunol. *10*, 925.

Vitale, I., Manic, G., Coussens, L.M., Kroemer, G., and Galluzzi, L. (2019). Macrophages and metabolism in the tumor microenvironment. Cell Metab. *30*, 36–50.

Wang, R., Dillon, C.P., Shi, L.Z., Milasta, S., Carter, R., Finkelstein, D., McCormick, L.L., Fitzgerald, P., Chi, H., Munger, J., and Green, D.R. (2011). The transcription factor Myc controls metabolic reprogramming upon T lymphocyte activation. Immunity *35*, 871–882.

Warburg, O. (1956). On the origin of cancer cells. Science *123*, 309–314.

Weinberg, F., Ramnath, N., and Nagrath, D. (2019). Reactive oxygen species in the tumor microenvironment: an overview. Cancers (Basel) *11*, 1191.

Wejksza, K., Lee-Chang, C., Bodogai, M., Bonzo, J., Gonzalez, F.J., Lehrmann, E., Becker, K., and Biragyn, A. (2013). Cancer-produced metabolites of 5-lipoxygenase induce tumor-evoked regulatory B cells via peroxisome proliferator-activated receptor α. J. Immunol. *190*, 2575–2584.

Wenes, M., Shang, M., Di Matteo, M., Goveia, J., Martín-Pérez, R., Serneels, J., Prenen, H., Ghesquière, B., Carmeliet, P., and Mazzone, M. (2016). Macrophage metabolism controls tumor blood vessel morphogenesis and metastasis. Cell Metab. *24*, 701–715.

Yan, D., Adeshakin, A.O., Xu, M., Afolabi, L.O., Zhang, G., Chen, Y.H., and Wan, X. (2019). Lipid metabolic pathways confer the immunosuppressive function of myeloid-derived suppressor cells in tumor. Front. Immunol. *10*, 1399.

Yang, M., Ma, C., Liu, S., Shao, Q., Gao, W., Song, B., Sun, J., Xie, Q., Zhang, Y., Feng, A., et al. (2010). HIF-dependent induction of adenosine receptor A2b

skews human dendritic cells to a Th2-stimulating phenotype under hypoxia. Immunol. Cell Biol. *88*, 165–171.

Zaiatz-Bittencourt, V., Finlay, D.K., and Gardiner, C.M. (2018). Canonical TGF-β signaling pathway represses human NK cell metabolism. J. Immunol. *200*, 3934–3941.

Zaynagetdinov, R., Sherrill, T.P., Gleaves, L.A., McLoed, A.G., Saxon, J.A., Habermann, A.C., Connelly, L., Dulek, D., Peebles, R.S., Jr., Fingleton, B., et al. (2015). Interleukin-5 facilitates lung metastasis by modulating the immune microenvironment. Cancer Res. *75*, 1624–1634.

Zelenay, S., van der Veen, A.G., Böttcher, J.P., Snelgrove, K.J., Rogers, N., Acton, S.E., Chakravarty, P., Girotti, M.R., Marais, R., Quezada, S.A., et al. (2015). Cyclooxygenase-Dependent Tumor Growth through Evasion of Immunity. Cell *162*, 1257–1270.

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. (2017). Enhancing $CD8^+$ T cell fatty acid catabolism within a metabolically challenging tumor microenvironment increases the efficacy of melanoma immunotherapy. Cancer Cell *32*, 377–391.e9.

Zhang, Y.X., Zhao, Y.Y., Shen, J., Sun, X., Liu, Y., Liu, H., Wang, Y., and Wang, J. (2019). Nanoenabled modulation of acidic tumor microenvironment reverses anergy of infiltrating T cells and potentiates anti-PD-1 therapy. Nano Lett. *19*, 2774–2783.

Zhao, Q., Chu, Z., Zhu, L., Yang, T., Wang, P., Liu, F., Huang, Y., Zhang, F., Zhang, X., Ding, W., and Zhao, Y. (2017). 2-deoxy-d-glucose treatment decreases anti-inflammatory M2 macrophage polarization in mice with tumor and allergic airway inflammation. Front. Immunol. *8*, 637.

Zhao, F., Xiao, C., Evans, K.S., Theivanthiran, T., DeVito, N., Holtzhausen, A., Liu, J., Liu, X., Boczkowski, D., Nair, S., et al. (2018). Paracrine Wnt5a-β-catenin signaling triggers a metabolic program that drives dendritic cell tolerization. Immunity *48*, 147–160.e7.

Zheng, Y., Delgoffe, G.M., Meyer, C.F., Chan, W., and Powell, J.D. (2009). Anergic T cells are metabolically anergic. J. Immunol. *183*, 6095–6101.

Zheng, X., Qian, Y., Fu, B., Jiao, D., Jiang, Y., Chen, P., Shen, Y., Zhang, H., Sun, R., Tian, Z., and Wei, H. (2019). Mitochondrial fragmentation limits NK cell-based tumor immunosurveillance. Nat. Immunol. *20*, 1656–1667.

Zheng, X., Zhang, N., Qian, L., Wang, X., Fan, P., Kuai, J., Lin, S., Liu, C., Jiang, W., Qin, S., et al. (2020). CTLA4 blockade promotes vessel normalization in breast tumors via the accumulation of eosinophils. Int. J. Cancer *146*, 1730–1740.

Zhou, X., Su, Y.X., Lao, X.M., Liang, Y.J., and Liao, G.Q. (2016). CD19(+)IL-10(+) regulatory B cells affect survival of tongue squamous cell carcinoma patients and induce resting CD4(+) T cells to CD4(+)Foxp3(+) regulatory T cells. Oral Oncol. *53*, 27–35.