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 neopeptopes 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 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 are correlated 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, acyl 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.

hypoxygen-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 T effector 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 T effector 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 T 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 ...
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 AAT inhibition by kynureninases and genetic ablation of HIF1α. Direct modulation targets immune cells, increasing nutrient availability and stimulating cytokine production. This leads to reduced immunosuppressive metabolites and decreased acidity and hypoxia in the TME.
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 immunomodulatory 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. Naïve 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...
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 (IFN-γ) 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 IC50 against PD-L1 on tumor cells, mTOR signaling is inhibited within these cells and their glycolytic turnover is reduced. Anti-tumor T effector 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 T 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) (Optitz 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 (Triplitt 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 glutaminase 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 blockade 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., 2019). 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-tumor 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 proteosomal 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 T effector 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<sub>2A</sub> extracellular adenosine receptor (A<sub>2AR</sub>) to inhibit the interleukin-2 (IL-2) upregulation and proliferation induced by TCR stimulation (Huang et al., 1997). A<sub>2AR</sub> 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<sub>2AR</sub> 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 lactate acidifier interferes with T cell survival and activation (Brand et al., 2016). Through NFAT downregulation, lactate inhibits IFN<sub>γ</sub> expression and curtails the anti-tumor response, allowing cancer growth and immune evasion. The motility of CD4<sup>+</sup> and CD8<sup>+</sup> 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 lactate 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<sup>+</sup> 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<sub>2</sub>) is a bioactive lipid metabolite synthesized by cyclo-oxygenase (COX). Once secreted into the TME by tumor cells, PGE<sub>2</sub> has immunosuppressive effects. PGE<sub>2</sub> signaling enhances Treg cell Foxp3 expression and activity, enhancing tumor growth (Sharma et al., 2005). PGE<sub>2</sub> may also inhibit IL-2 and IFN<sub>γ</sub> production by CD4<sup>+</sup> T cells (Snijderswint 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 (Keppl 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 IFN<sub>γ</sub> 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 transportsers SLC1A5 and CD98 (Jensen et al., 2017). The improved metabolic capacity is regulated by mTOR activation (Marcas 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<sup>+</sup>, 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 IFN<sub>γ</sub> production by CD4<sup>+</sup> T cells (Snijderswint et al., 1993). Clinical trials combining ICB with COX1/2 inhibitors, including acetylsalicylic acid (Aspirin), are currently under way (ClinicalTrials.gov ID NCT03638297).
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 (Maçais 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., 2016). 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; Zaaitz-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; Pötzi et al., 2017). Adenosine in the TME reduces NK cell function because its engagement of A2AR 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 (Stift 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 CD3; 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 immunosuppressive 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 PGE₂, 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 neangiogenesis 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 PGE₂ 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 inactivation of the master antioxidant transcription factor Nrfl2. MDSCs can also increase glycolysis to accumulate phospho-enoxyruvate (PEP), which is a ROS scavenger (Ohl et al., 2018). MDSCs can be targeted directly and rendered less suppressive by IDO, NOX, or Nrfl2 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 (Templet 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, PGE₂, 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 preferentially 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 PGE₂, 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 (Horii 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; Zaynaginov 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 glucose and glutamine. Whether these results translate accurately to the TME context requires more investigation, but the insights gained have opened up new research perspectives (Giovannelli 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 accumulates 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 PGE2, 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 A2B5R, leading to IL-10 and IDO production (Gottfried et al., 2010).
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-tumor 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 re-programming 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 under-studied 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-tumorogenic 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 Hif1α 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
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 (Dell’offe 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 develop future durable and effective immunotherapies (Qiu et al., 2019).

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 efficacy 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 in vitro 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 synergistic 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

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**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.
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 (Gopala-krishnan 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 immunity 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.

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