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Targeting Metabolism to Improve the Tumor Microenvironment for Cancer Immunotherapy

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Abstract

The growing field of immune metabolism has revealed promising indications for metabolic targets to modulate anti-cancer immunity. Combination therapies involving metabolic inhibitors with immune checkpoint blockade (ICB), chemotherapy, radiation, and/or diet now offer new approaches for cancer therapy. However, it remains uncertain how to best utilize these strategies in the context of the complex tumor microenvironment (TME). Oncogene-driven changes in tumor cell metabolism can impact the TME to limit immune responses and present barriers to cancer therapy. These changes also reveal opportunities to reshape the TME by targeting metabolic pathways to favor immunity. Here we explore current strategies that shift immune cell metabolism to pro-inflammatory states in the TME and highlight a need to better replicate physiological conditions to select targets, clarify mechanisms, and optimize metabolic inhibitors. Unifying our understanding of these pathways and interactions within the heterogenous TME will be instrumental to advance this promising field and enhance immunotherapy.

Introduction

Cancer metabolism has been studied extensively over the past two decades and it is widely accepted that oncogenic transformation can cause cancer cells to adapt a well-characterized metabolic phenotype that can profoundly influence the tumor microenvironment (TME) (Vander Heiden & DeBerardinis, 2017). The TME is composed of diverse cell populations in a complex matrix, which often has limited or poorly differentiated vasculature, creating inefficiencies of nutrient and/or oxygen delivery as well as waste removal. This poor vascular exchange can result in nutrient limitation in the TME, while the bioenergetic demands of rapidly proliferating cancer and immune cells compete for nutrients necessary to carry out an anti-tumor defense (De Berardinis & Chandel, 2016; Pavlova & Thompson, 2016). In these settings, the metabolic microenvironment of tumors themselves can present

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an immune suppressive environment to be overcome. Notably, this harsh environment forces infiltrating immune cells to undergo metabolic adaptations associated with tolerant phenotypes. Ultimately these metabolic changes in immune cells can undermine the effectiveness of the anti-tumor immune response.

Strategies to alter cell metabolism now offer promising opportunities for cancer therapies. Specifically, identifying targets that suppress or alter cancer metabolism to improve the TME nutrient availability or that modulate immune metabolism to bolster inflammation will help maximize the efficacy of cancer therapies. A key barrier is that many metabolic pathways used by cancer cells are also important for inflammatory immune function and blocking those pathways may be counterproductive. Further, many metabolic pathways can have context specific effects, such that different microenvironments may lead to different outcomes. Despite these apparent challenges, *in vitro* models that enforce assay uniformity are often used to identify metabolic targets which then often fail to translate to the heterogenous TME *in vivo* or in diverse cancer types or patients. The inability to replicate physiologic conditions *in vitro* and lack of relevant *ex vivo* model systems thus ultimately delays the development of effective treatments. This review explores current strategies and molecular targets under investigation to modulate immune metabolism in the TME and describe the limitations of *in vitro* culture conditions in metabolic studies. Improving our understanding of these therapeutic targets through both mechanistic and global systems-level views of the heterogenous TME will help advance the translation of these approaches.

Metabolic profiles and nutrient requirements of activated immune cells

Immune cells develop specific metabolic profiles during times of activation, adaptation to different tissue environments, and during periods of inflammation or disease (Andrejeva & Rathmell, 2017). Importantly, metabolic changes also occur within immune cells following migration into a TME. Different types and subsets of immune cells have distinct nutrient requirements for their metabolic programming and therefore are faced with unique challenges upon migration to the TME (Figure 1).

T cell subsets serve as well-characterized examples of these adaptations within a TME due to their distinct metabolic programs. Briefly, activated T cells ramp up both glycolytic and glutaminolytic metabolism, preferentially using aerobic glycolysis over TCA-coupled OXPHOS for ATP production and biosynthesis for clonal expansion (E. L. Pearce, Poffenberger, Chang, & Jones, 2013). Activation with CD28 co-stimulation, however, can increase spare mitochondrial capacity and enhance respiration under low glucose conditions (Frauwirth et al., 2002; Klein Geltink et al., 2017). By contrast, regulatory T cells (Tregs) rely on OXPHOS and fatty acid oxidation (FAO) to support their survival and differentiation (Beier et al., 2015; P. C. Ho & Liu, 2016; Michalek et al., 2011) and may uniquely activate AMPK signaling that promotes mTOR Complex I activity to drive catabolic processes (Delgoffe et al., 2009; Kishton et al., 2016).

Myeloid cells also exhibit characteristic metabolic phenotypes upon activation. Tumor antigens activate DCs through Toll-like receptor (TLR) signals which lead to rapid increases in glycolysis and fatty acid synthesis (FAS). DCs remain glycolytic, which is essential for

continued survival and is controlled by mTOR and hypoxia-inducible factor 1α (HIF1α) (E. J. Pearce & Everts, 2015). Similarly, macrophages reprogram their metabolism in response to TME through activated glycolysis, FAS and altered nitrogen cycle metabolism while maintaining a tumor promoting function of cytokine production and angiogenetic factor secretion. Tumor associated macrophages (TAMs) are categorized into M1-like and M2-like phenotypes, although this dichotomy does not fully appreciate the heterogeneity of TAM subsets. M1-like TAMs reflect a more inflammatory phenotype and use glycolysis, FAS and amino acid metabolism to support their function. Conversely, M2-like TAMs exhibit a more suppressive phenotype, utilizing the TCA cycle and FAO (Netea-Maier, Smit, & Netea, 2018). Of note, however, limited information is available on human macrophage phenotypes and macrophage metabolism data have been largely derived from murine studies. Despite this, there appears to be a clear distinction between the metabolic programs of M1-like and M2-like TAMs which could pose unique targeting strategies requiring further investigation in primary human macrophages (Al-Khami, Rodriguez, & Ochoa, 2017).

Neutrophils and myeloid derived suppressor cells (MDSC) have complex roles in the TME that can promote cancer progression. Neutrophils are often described as purely glycolytic to support ATP generation and microbial killing. However, under glucose-restricted conditions as may occur in TMEs, neutrophils engage in oxidative mitochondrial metabolism and FAO to support NADPH oxidase-dependent ROS production (Rice et al., 2018). Although neutrophils are generally inflammatory they have been implicated in cancer progression, possibly through association or plasticity to MDSCs (Rapoport, Steel, Theron, Smit, & Anderson, 2020), which can potently suppress innate and adaptive immunity. The MDSC subset of myeloid cells and their metabolic profile has yet to be fully characterized but are considered a therapeutic target particularly within tumors. *In vitro* generated MDSCs display an increase in glycolysis, glutaminolysis, and TCA cycle activity with an increased AMPK activation (Hammami et al., 2012). Interestingly, MDSCs *in vivo* display unique phenotypes depending on tissue origin and microenvironment. For example, tumor-infiltrating MDSCs have increased mitochondrial mass and preferentially use FAO over glycolysis as a primary source of energy compared to peripheral MDSCs (Al-Khami, Rodriguez, & Ochoa, 2016; Hossain et al., 2015). Recently, the glycolytic by-product methylglyoxal has been identified as a more specific marker for MDSCs and may play a key role in the suppression of T effector function (Baumann et al., 2020).

Targeting hypoglycemia within the TME

The enhanced glycolytic activity of cancer cells combined with poor vascular exchange may result in a limited availability of glucose within the TME, although this depends on tumor type. While glucose can be available in some tumors (Siska et al., 2017), it may be partially depleted in the interstitial fluid of others compared to plasma or healthy tissue (M. R. Sullivan et al., 2019). Co-culture of lymphoma cells and T cells revealed that lymphoma cells impose a nutrient deprivation or a metabolic competition on T cells that limits their ability to produce effector cytokines (C.-H. Chang et al., 2013; C. Chang et al., 2015). Reduced glucose availability can limit T cell expansion and effector function through competition, altered apoptosis sensitivity (Voss, Larsen, & Snow, 2017), or lead to eventual “exhaustion”. Low glucose environments also induce FOXP3 expression, increasing T cell

differentiation from effector T cells to Tregs (Macintyre et al., 2014). Additionally, accelerated glycolytic metabolism in cancer cells increases tumor-derived granulocyte-macrophage colony-stimulating factor (CSF) and macrophage CSF to promote infiltration of MDSCs, which further suppress effector T cell function (W. Li et al., 2018).

Targeting low glucose availability in the TME has had mixed results. Reducing glycolytic metabolism in cancer cells by either inhibiting glycolytic regulatory enzymes or using the competitive glucose analog 2-DG may be effective at reducing cancer cell proliferation and has been shown to support the formation of long term memory CD8+ T cells, but can also suppress the proliferation and function of tumor infiltrating effector immune cells (Bonuccelli et al., 2010; Kouidhi, Ayed, & Elgaaied, 2018; Sukumar et al., 2013; D. Zhang et al., 2014). For example, Ho et. al discovered that overexpression of a gluconeogenic enzyme PCK1 can improve T cell antitumor responses upon infiltration into a glucose deprived TME (P.-C. Ho et al., 2015) to support an important role for glycolytic intermediates in the proliferation and function of effector T cells. Most recently, neutralization of the dicarbonyl activity of methylglyoxal produced by MDSC could improve efficacy of cancer immune therapy (Baumann et al., 2020).

Many studies have indicated that immune checkpoints including as PD-1, PD-L1 and CTLA-4 act in part by suppressing metabolic reprogramming of immune cells and inhibit glycolysis while increasing lipolysis and FAO (Parry et al., 2005; Patsoukis et al., 2015; Qorraj et al., 2017). Blockade of these pathways with checkpoint inhibitors thus rescue the effector function of tumor infiltrating lymphocytes (TILs) in part by restoring glycolysis and favorable anabolic metabolic pathways (Figure 2). Consistent with this model for checkpoint action, antibodies against CTLA-4, PD-1, and PD-L1 corrected tumor-induced glucose restrictions on T cell metabolism, restored T cell glycolysis, and IFN-γ production (C. Chang et al., 2015). However, the effects of checkpoint blockade therapy on the metabolism of other immune cells warrants further attention. For example, myeloid cell-specific ablation of PD-1 more effectively decreased tumor growth than T cell-specific ablation, yet the metabolic impact of PD-1 blockade on myeloid cells remains uncertain (Strauss et al., 2020).

Although the use of checkpoint blockades has greatly improved cancer therapy outcomes, it is important to note that the current strategies have been most effective against highly glycolytic tumors (Darvin, Toor, Sasidharan Nair, & Elkord, 2018; Najjar et al., 2019) which are characterized by a high neoantigen load, high levels of TILs, low MDSCs and increased secretion of IFN-γ. In contrast, poor responsiveness to PD-1 blockade may correlate less well with the extent of tumor glycolysis than high rates of tumor oxidative phosphorylation (Najjar et al., 2019). These data show clear links between cell metabolism and checkpoint blockades such that combinations with metabolic interventions to disrupt cancer metabolism may offer opportunities to increase the efficacy of checkpoint inhibitors across diverse tumor types. It is important to consider that each of these targets can have differential effects and are cell subset and context dependent.

Targeting Lactate in the TME

Enhanced glycolytic activity of cancer cells under hypoxic conditions increases the buildup of lactate which acidifies the TME (Brand et al., 2016; Choi, Collins, Gout, & Wang, 2013; Colegio et al., 2014). Lactate production can be increased 40-fold in tumor cells, and the lactate producing enzyme lactate dehydrogenase (LDH) is positively correlated with tumor size and clinical severity (Girgis et al., 2014; X. Sun et al., 2014). Lactic acid can inhibit effector T cell function through decreased proliferation and IFN-y production (Fischer et al., 2007; Mendler et al., 2012) and decrease the pH within the TME to further contribute to immune suppression. Low pH was also found to dramatically promote the differentiation of monocyte derived dendritic cells which exhibit reduced glucose consumption, upregulated mitochondrial respiration genes and inhibited mTORc1 activity (Erra Díaz et al., 2020). Hence, neutralization of low pH in the TME may have a meaningful impact on improving the efficacy and outcomes of anticancer immunotherapy (Figure 2). Notably, buffering the TME with oral bicarbonate can inhibit tumor growth when combined with anti-PD-1 immunotherapy in a melanoma model, and improve survival when combined with adoptive T-cell transfer (Koltai, 2016; Kouidhi et al., 2018). More recently, VISTA was found to selectively suppress T cells under acidic pH and that the development of acid pH selective antibodies against VISTA or its receptor, PSGL-1, reversed immune suppression *in vivo* (Johnston et al., 2019). In addition, co-blockade of VISTA and PD-1 resulted in tumor rejection within the MC38 tumor model. This work supports a promising approach that exploits the acidic TME to improve the selectivity of treatments and enhance ICB therapy.

In addition to maintaining physiologic pH in the TME, lactate accumulation also has direct immunosuppressive effects on immune cells. First, lactate inhibits monocyte activation and dendritic cell differentiation (Gottfried et al., 2006; Nasi et al., 2013) and promotes M2-polarization through increased arginase and HIF-1α stabilization (Colegio et al., 2014). Lactate also inhibits NK cell function and increases MDSCs further contributing to the suppressive microenvironment (Husain, Huang, Seth, & Sukhatme, 2013). Additionally, cancer cell-generated lactate activates the G protein coupled receptor (GPR81) on immune cells and endothelial cells, which promotes angiogenesis and immune evasion (Brown & Ganapathy, 2019). Knockdown of this signaling pathway in mice reduced the production of IL-10 and suppressed the generation of Tregs (Feichtinger & Lang, 2019; Ranganathan et al., 2018). Finally, lactic acid can also boost Treg survival in the TME given their robust ability to oxidize exogenous lactate (Angelin et al., 2017). These data suggest that targeting lactate-responsive pathways or receptors such as GPR81 may provide a promising approach to cancer therapeutics (Faubert et al., 2017).

One target of particular interest is the lactate producing enzyme lactate dehydrogenase (LDH). Targeting LDH has shown promising anticancer effects (Yeung et al., 2019), but can have differential effects to immune cell function. While inhibition of LDH using small-molecules or siRNA may ameliorate intratumor lactate levels and tumor regression (de la Cruz-López, Castro-Muñoz, Reyes-Hernández, García-Carrancá, & Manzo-Merino, 2019), these preclinical results require additional study. Additionally, LDH inhibition can lead to a decrease in T cells and IFN-γ production (Kouidhi et al., 2018). While inhibition of lactate

may provide a novel therapeutic in cancer, clinical evaluation of these drugs and contradictory effects on immune function must be considered.

A different approach to targeting lactate is to inhibit lactate transporters. To this end, monocarboxylate transporter (MCT) 1 and/or 4 inhibitors have been effective at increasing intracellular lactate and resulted in decreased glycolytic rate with enhanced cell death of cancer cell lines (de la Cruz-López et al., 2019). These treatments have been reported to enhance IL-2 and IFN-γ secretion in T cells (Chirasani et al., 2012), suggesting that MCT disruptors could suppress tumor cell proliferation while supporting T cell activation (Kouidhi et al., 2018). Redundancy between these two transporters, however, makes a dual strategy likely necessary to achieve significant broad impact. For example, dual inhibition of MCT 1 and 4 with syrosingopine showed promise in combination with metformin by causing a lethal energy crisis in cancer cells (Benjamin et al., 2018).

Targeting amino acid metabolism

Amino acids provide components and substrates for a variety of critical processes in cell metabolism and physiology. While each individual amino acid plays multiple specific roles, glutamine, arginine, and tryptophan have been best described to modulate both tumor progression and immunity (Figure 3).

Glutamine and Glutamate

After glucose, glutamine is the most abundant amino acid in circulation and the most rapidly consumed nutrient by many cultured cancer cells and (Lukey, Katt, & Cerione, 2017). Glutamine is used as an anaplerotic fuel source to maintain TCA flux in cancer cells undergoing aerobic glycolysis or can be used in reductive carboxylation as a source of citrate for lipid synthesis. Additionally glutaminolysis can suppress oxidative stress, and maintain mitochondrial membrane integrity contributing to the survival of proliferating cells (Ananieva, 2015). Glutaminase (GLS) converts glutamine to glutamate and is now being targeted to suppress the metabolism of some cancers (Bott, Maimouni, & Zong, 2019; Ren et al., 2020). Blocking GLS activity can reduce glutamate which leads to redox and mitochondrial stress, to which cells respond with an increased dependence on aspartate as a means to regenerate glutamate and maintain cellular redox (Alkan et al., 2018). Targeting this pathway may also decrease cancer cell glucose consumption. However, resistance to GLS inhibition in some cancers is mediated by adapting mechanisms which increase glucose metabolism to anaplerotically maintain mitochondrial flux.

Unlike glucose which is required by both cancer and immune cells for anabolic growth, glutamine may be differentially utilized by cancer and immune cells. Interestingly, inflammatory anti-tumor immune cells appear to be less dependent or even restrained by this pathway. Macrophage subsets demonstrate inherent differences in their dependencies for glutamine. For example, M2 macrophages consume more glutamine than naive macrophages while, pro-inflammatory M1 macrophages can be suppressed by glutaminolysis (P. S. Liu et al., 2017). This differential effect appears in part due to a product of glutaminolysis, α-KG, which can change gene expression programs to favor more anti-inflammatory M2 like states. In a breast cancer model, inhibiting glutamine metabolism, decreased tumor growth through

reduced MDSC recruitment and promoted their conversion to inflammatory M1 like macrophages (Oh et al., 2020). Additionally, reducing intracellular glutamine in macrophages through inhibition or genetic ablation of glutamine synthetase (GLUL) promoted an M1-like phenotype consistent with enhanced glycolysis and subsequent activation of HIF-1α (Bott et al., 2019; Palmieri et al., 2017). These data suggest that targets aimed at inhibiting glutaminolysis or reducing intracellular glutamine can inhibit suppressive myeloid subsets and provide a potential target that repolarizes TAMs from M2-like into M1-like states.

Glutamine metabolism is also increased in effector T cell activation to provide intermediates necessary for growth (O'Neill, Kishton, & Rathmell, 2016). Deprivation of glutamine has been found to alter Th1 differentiation and shift naïve CD4+ T cells towards a Treg phenotype (Klysz et al., 2015). Additionally, genetic loss of the glutamine transporter protein ASCT2 in T cells resulted in impaired generation and function of Th1 and Th17 cells, whereas Tregs were not altered (Nakaya et al., 2014). Blockade of glutamine metabolism via GLS targeting to prevent glutamine-dependent production of glutamate, however, lead to adaptive subset-specific metabolic reprogramming in T cells to differentially regulate survival, proliferation, and effector function. While Th17 cells remain dependent on GLS and were suppressed by GLS inhibition or genetic deletion, Th1 and cytotoxic T cells adapted to become GLS-independent through upregulation of glycolysis (Araujo, Khim, Mkhikian, Mortales, & Demetriou, 2017; Johnson et al., 2018; Kono et al., 2019). Indeed, broad blockade of glutamine metabolism combined with anti-PD-1 dramatically improved antitumor effects by suppressing tumor metabolism while promoting T cell glucose metabolism, epigenetic reprogramming, and cytotoxic function (Leone et al., 2019). When tested in a Chimeric Antigen Receptor (CAR)-T cell model, however, genetic deletion of GLS enhanced effector differentiation but eventually led to loss of T cell effector function (Johnson et al., 2018). This effect appeared in part due to terminal T cell effector differentiation or potential suppression of T cells through induction and activation of inhibitory receptors including PD-1. Together, studies of glutamine metabolism do highlight a potential method to separate the distinct dependencies of cancer cells and inflammatory immune cells that may allow specific immune cell targeting in immunotherapy.

Arginine and Nitric Oxide

Arginine plays important roles in a variety of biological functions including proliferation, survival and protein synthesis in both cancer and immune cells. CD8+ T cells especially benefit from L-arginine uptake by enhanced survival, memory formation and anti-tumor efficacy (Geiger et al., 2016). Arginine metabolism predominately relies on the activity of nitric oxide synthetase (NOS) and arginase (ARG) enzyme families. Due to its dual roles in both cancer and immune cells, the modulatory effect of arginine within the TME is complicated. Depletion of arginine is generally well tolerated and has been shown to have anti-tumor effects in arginine-dependent cancer types. However, many cancer cells can activate the arginine-succinate synthetase (ASS1) pathway to synthesizes arginine from citrulline to compensate for arginine starvation (Mondanelli, Iacono, Allegrucci, Puccetti, & Grohmann, 2019; Zou, Wang, Liu, Ke, & Xu, 2019). Despite being effective in some cancer types, arginine depletion can also negatively impact the immune response through increasing

accumulation of MDSCs and inhibiting T cell function (Raber, Ochoa, & Rodríguez, 2012). More specifically, MDSCs expressing ARG contribute to arginine depletion in a TME to suppress antitumor T cell responses (Fletcher et al., 2015). Furthermore, increased lactate in the TME favors the catabolism of arginine by ARG over NOS, resulting in increased TAM secretion of tumor-supporting factors (Carmona-Fontaine et al., 2017; Colegio et al., 2014). Indeed, inhibiting ARG can restore arginine levels resulting in tumor regression and improved T cell function (Miret et al., 2019).

Alternatively, metabolism of arginine through NOS results in the release of NO and generally promotes an inflammatory phenotype in myeloid cells. Macrophage-derived NO induces the expression of the adhesion molecule VCAM-1 in melanoma xenografts, which is important for T-cell extravasation. In addition, NO produced by tumor-infiltrating myeloid cells was found to be important for activation of adoptively transferred cytotoxic T cells (Marigo et al., 2016). Co-transfer of CD8+ T cells with wild-type macrophages, but not with NOS-depleted macrophages, increased T-cell homing to the tumor and consequently enhanced to tumor rejection (Keshet & Erez, 2018; Sektioglu et al., 2016). Taken together these studies suggest that targeting ARG and NOS activity in myeloid cells could provide a potential for immune therapies in cancer, although the mechanisms of ARG and NOS in immune cell regulation need further elucidation.

Tryptophan and kynurenine

Unlike glutamine and arginine, tryptophan in an essential amino acid that must be taken from the diet to support physiological processes including cell growth and maintenance. Tryptophan also acts as the substrate for the kynurenine pathway dictated by the rate limiting enzymes indoleamine-2,3-dioxygenase (IDO1), IDO2 and tryptophan-2,3-dioxygenase (TDO). In cancer, dysregulated IDO1 and TDO activation may suppress antitumor immunity. In addition to potential tryptophan depletion, kynurenine can accumulate in IDO positive cancers and is, in turn, associated with poor prognosis in cancer patients (Heng et al., 2016; Ino et al., 2008; Platten, Nollen, Röhrig, Fallarino, & Opitz, 2019). Specifically, increased kynurenine correlates with defective interleukin-2 (IL-2) signaling in memory CD4+ T cells. Increased IDO1 activity prevents the activation of effector T cells, inhibits NK cell function, supports Treg activation, and promotes the expansion and activation of DCs and MDSCs (Fallarino et al., 2003, 2006; Frumento et al., 2002; Munn et al., 2005). Despite this promising pre-clinical data suggesting inhibiting IDO or reducing kynurenine may improve immune function within the TME, IDO inhibitors showed disappointing efficacy in monotherapy clinical trials (Labadie, Bao, & Luke, 2019).

IDO inhibitors may, however, still provide benefit in some combinations with chemotherapy, radiotherapy, or other immunotherapy. Indeed, IDO1 inhibitors have been investigated as a metabolic adjuvant for immune cells to boost anti-tumor immunity (M. Liu et al., 2018) and are currently under being evaluated in combination with anti-PD-1 or anti-CTLA-4 in a number of cancer settings. Previously, IDO1 inhibition combined with anti-PD-1 improved objective response rates in unresectable stage 3 and 4 melanoma patients (Lanitis, Dangaj, Irving, & Coukos, 2017). In a murine tumor model, the combination of an IDO inhibitor with an anti-tumor dendritic cell vaccine resulted in conversion of Tregs into Th17 cells that

enhanced CD8+ T cell anti-tumor function (Riera-Domingo et al., 2020; Sharma et al., 2009). This area remains controversial but highlights the need for effective and physiologically relevant pre-clinical studies to best identify the conditions in which IDO1 inhibitors and modulation of tryptophan metabolism in the TME may add therapeutic value.

Targeting Fatty Acid Metabolism

Highly proliferative cancer cells show a strong lipid and cholesterol avidity, which they satisfy by either increasing uptake of exogenous lipids or hyper-activating synthesis pathways. Indeed, many cancer cells have been found to upregulate enzymes involved in lipid and cholesterol biosynthesis (Beloribi-Djefaflia, Vasseur, & Guillaumond, 2016; Wegiel, Vuerich, Daneshmandi, & Seth, 2018). Excessive lipids and cholesterol are stored in lipid droplets, which are quantitatively correlated with cancer aggressiveness (Beloribi-Djefaflia et al., 2016). For these reasons, inhibitors of fatty acid synthesis (FAS) have been an area of focus for cancer therapy, especially targeting of fatty acid synthase (FASN) (Lu et al., 2018; Mullen & Yet, 2015). However, inhibition of fatty acid metabolism in cancer cells will also have indirect consequences on immune cell function (Figure 4).

Fatty acids and lipid accumulation have individual consequences for different immune cell subsets, but lipid accumulation generally leads to immunosuppressive effects. In myeloid cells, intracellular accumulation of lipids enhances oxidative metabolism and promotes immunosuppressive function (Le Bourgeois et al., 2018). Presence of the unsaturated fatty acid oleate polarizes bone marrow-derived myeloid cells into an immunosuppressive M2 like TAM (Wu et al., 2019). Abnormal lipid accumulation of tumor infiltrating DCs (TIDCs) impairs their antigen presentation (Herber et al., 2011). In a murine model of ovarian cancer, TIDCs accumulated excess lipids exogenously from the TME resulting in poor T cell priming and activation (Jiang, Fang, Wang, Li, & Wang, 2018). Accumulation of fatty acids therefore has direct consequences within the immune cell populations in the TME, and strategies aimed to ameliorate lipid abundance either through targeting FAS or FAO have been beneficial in murine tumor models. For example, inhibition of FAS by an acetyl-CoA carboxylase (ACC) inhibitor, TOFA, normalized lipid levels in DCs to restore their activity and substantially enhanced the effects of a cancer vaccine (Herber et al., 2011). Inhibition of FASN also showed partial rescue of TIDC function in an ovarian cancer model (Jiang et al., 2018). Alternatively, inhibition of FAO may limit the immunosuppressive function of M2 macrophages (Q. Zhang et al., 2018).

Targeting fatty acid metabolism in T cells may allow for tuning of the T cell response by eliciting different effects in distinct T cell populations. On the one hand, FAO is needed for the development of CD8+ memory cells (D. O. Sullivan et al., 2014), however it is also important for the differentiation of Tregs. Thus, FAO blockade could prevent the accumulation of this immunosuppressive T cell population (Beier et al., 2015; Michalek et al., 2011) In mouse melanoma models, CD8+ TILs enhanced PPAR-α signaling and catabolism of fatty acids to preserve their effector functions (Y. Zhang et al., 2017), suggesting fatty acid uptake could be beneficial in certain TMEs. However, it has been recently found that the lipid transporter CD36 promotes Treg survival and function in tumors (Wang et al., 2020). Further inhibition of the fatty acid binding protein exclusively expressed

in T cells, FABP5, enhances Treg suppression (Field et al., 2020). In a study of fatty acid metabolism and apoptosis sensitivity in primary human T cells, inhibition of FASN with C75 or siRNA knockdown significantly protected T cells from restimulation-induced cell death (RICD) by reducing the induction of FAS Ligand (Voss, Luthers, Pohida, & Snow, 2019). Therefore, FASN inhibition could be used to protect T cells from apoptosis in the TME caused by repeated TCR activation and boost T cell immunity in addition to its anti-tumor efficacy on cancer cells directly. Additionally, disruption of FAO was dispensable for RICD, highlighting the specificity of different fatty acid metabolism pathways in programming apoptosis sensitivity of immune cells. Although in a separate study, FAO inhibition exhibited delayed tumor growth and enhanced anti-tumor efficacy of T cells (Q. Zhang et al., 2018). Lipid and cholesterol metabolism are clearly complex but do offer intriguing opportunities to modulate the TME and specific immune cell populations.

Targeting Nutrient and Oxygen Sensing Pathways in the TME

AMPK

One approach to modify glucose metabolism in the TME is to focus on signaling pathways that respond to altered nutrient availability and regulate cell metabolism and fate (Figure 2). In low glucose environments, the cellular AMP:ATP ratio shifts as ATP levels decrease to activate the 5’-AMP-activated Protein Kinase (AMPK), which then induces a metabolic switch toward catabolism and OXPHOS (Eichner et al., 2019). High glucose consumption in the TME that exceeds the vascular exchange capacity may promote AMPK activation, which may aid the persistence of suppressive immune cells including TAMs, MDSCs, and Tregs (Blagih et al., 2015; Eichner et al., 2019; Michalek et al., 2011; Siska & Rathmell, 2015). Tregs specifically depend on an OXPHOS-dominant metabolism in order to function in glucose-limited, lactate-rich environments (Angelin et al., 2017). Effector T cells can also be limited by AMPK activation, through inhibition of the mTORC1 pathway and catabolic metabolism (Ma, Poffenberger, Wong, & Jones, 2017). Furthermore, AMPK activation in DCs can hinder their ability to elicit CD8+ T cell activation (Challier, Bruniquel, Sewell, & Laugel, 2013; Giovanelli, Sandoval, & Cubillos-Ruiz, 2019).

AMPK activity must be balanced, however, as while excessive AMPK may inhibit effector T cell responses, disabling AMPK activation may enhance glycolysis and inflammation while sensitizing cells to metabolic stress. In support of role, AMPKα-deficient macrophages and DCs exhibit heightened inflammatory function through increased production of inflammatory cytokines and an enhanced capacity for antigen presentation favoring the promotion of Th1 and Th17 responses (Carroll, Viollet, & Suttles, 2013). Similarly, AMPKα-deficient T cells exhibit increased glycolysis and elevated interferon-γ (IFN-γ) production (MacIver et al., 2011). However, AMPK-deficient T cells also became more sensitive to stress and apoptosis, as shown by their decreased efficacy *in vivo* in settings such as lung inflammation (Blagih et al., 2015). These studies suggest that AMPK disruption has shown promise to promote inflammation but may limit survival of inflammatory cells and should be carefully balanced.

One of the most well-known drugs to target AMPK is metformin, which activates AMPK signaling and is widely used for diabetes. In mice, metformin treatment can reduce the risk

of certain cancers and decrease tumor burden in breast cancer models (Anisimov et al., 2005; Bodmer, Meier, Krähenbühl, Jick, & Meier, 2010). In human cohorts, metformin has also shown particular promise in colorectal cancer patients, although these analyses are complicated by comorbidities such as diabetes (Cheng et al., 2020). AMPK activation is thought to reduce tumor burden in part by slowing tumor growth, while concurrently supporting the expansion and survival of TIL in the TME (Blagih et al., 2015; Eikawa et al., 2015; Wegiel et al., 2018). Of note, metformin can also reduce glycolytic flux of cancer cells by blocking phosphofructokinase-1 (PFK1) (Hu et al., 2019) and other glycolytic enzymes induced by HIF-1α (Tyszka-Czochara, Bukowska-Strakova, Kocemba-Pilarczyk, & Majka, 2018). In multiple mouse models of AMPK-deficient leukemia, increased tumor cell death and mouse survival was observed (Chan et al., 2017; Kishton et al., 2016; Saito, Chapple, Lin, Kitano, & Nakada, 2015). Thus, while AMPK signaling may support survival of suppressive immune cell populations, it may also mitigate cell stress to support cancer cell survival. The conflicting outcomes of AMPK manipulation show that the AMPK pathway plays an important role in the TME, although it moderates a context and time dependent balance over cancer cell stress and anti-tumor immunity. Therefore, AMPK-directed therapeutics must consider both the direct effects on cancer cell death as well as the immune cell phenotype effects within the TME.

mTOR

The mTOR pathway also senses nutrients and plays a central role to promote glucose and anabolic metabolism while opposing AMPK. mTOR complex 1 (mTORC1) becomes activated in response to increased levels of glucose and amino acids, such as the essential amino acids leucine and isoleucine, to promote protein synthesis, cell proliferation and growth pathways that are important for immune cells and many cancer cell types (Saxton & Sabatini, 2017). In T cells, mTORC1 sustains glycolysis and cytokine-driven differentiation and T cell subset effector functions. Similar to the AMPK pathway, mTOR signaling occurs in a cell specific and context dependent manner which may present many challenges in the use of targeted immunotherapy in cancer. For example, the mTORC1 inhibitor rapamycin enhances CD8+ memory T cell formation (Araki et al., 2009), but is immune suppressive and abolished CD8+ antitumor responses in combination with vaccine therapy (Chaoul et al., 2015). Conversely, Treg suppressive activity can be impaired by over-activation of mTORC1 activity yet is enhanced by low levels of mTORC1 (Chapman et al., 2018; Gerriets et al., 2016). Although inhibiting mTORC1 may boost cancer therapy short-term, it raises the possibility of developing autoimmunity long-term, because the generation of effector Tregs (eTregs) is dependent on mTORC1 signaling (I.-H. Sun et al., 2018). It is important to find the right mTORC1 activity level conducive for memory formation without compromising effector T cells activity or promoting Treg. Whereas mTOR targeting in macrophages also appears to be complex and context-dependent, NK cells may offer the most promising target for mTORC1 mediated antitumor effects. Mao et al found that a high dose of IL-15 activates mTORC1 to sustain NK cell development and proliferation, and suggest that adoptive transfer of IL-15 primed NK cells could be applied clinically (Mao et al., 2016; Marçais et al., 2014). Rapamycin analogues (rapalogues) are approved for cancer therapy and can reduce cancer aerobic glycolysis and growth. These treatments, however, may not only suppress anti-tumor immunity, but also have the potential to actively promote

immune suppressive environments. Similar to AMPK pathway, targeting mTOR pathway will require a nuanced approach to elicit beneficial immune responses without leading to a tumor protecting immune environment.

Hypoxia and HIF1-α in TME

Hypoxia itself has been shown to inhibit the differentiation, proliferation and IFN-γ production of T effector cells (Cho et al., 2016; Westendorf et al., 2017). Importantly, TCR activation upregulates hypoxia inducible factor (HIF) expression in CD4+ T cells, and is required for glycolytic flux and inflammation during hypoxic conditions (Chen et al., 2020; Cho et al., 2019). In reduced oxygen conditions, such as an inadequately vascularized TME, HIFs are stabilized to promote the transcription of glycolytic genes and cytokines that promote anaerobic metabolism and angiogenesis. HIF-1 and HIF-2 are attractive targets to suppress tumor metabolism by blocking this physiological response to inadequate oxygenation yet can also strongly influence potential anti-tumor responses (Figure 5). Furthermore, inadequate vascularization of some TMEs contribute to dysregulated immune cell trafficking. Hypoxia itself has conflicting effects on the function of CTLs. For example, HIF-1α-deficient CD8+ T cells had reduced tumor infiltration and killing, whereas activation in reduced oxygen conditions could enhance subsequent anti-tumor function (Gropper et al., 2017; Palazon et al., 2017). Treg are also sensitive to hypoxia and may be enhanced under low oxygen condition, as HIF-1α can bind to the promoter region of the Treg transcription factor, FOXP3, in CD4+ T cells to increase transcription and was required for Treg suppression *in vivo* (Clambey et al., 2012). Conversely, loss of HIF-1α in Tregs under hypoxic conditions also resulted in increased suppressive capacity, suggesting that targeting and complete loss of HIF-1α in Tregs could enhance suppressive function and impair anti-tumor immunity (Miska et al., 2019). This dual regulation of Treg function may be due in part to changes in mitochondrial pyruvate uptake and oxidative metabolism, which is consistent with increased Treg function in elevated lactate (Angelin et al., 2017).

Intratumoral hypoxia alters other tumor-associated immune cells to favor immunosuppressive phenotypes. HIF-1α induced arginase activity and production of nitric oxide in MDSCs leads to induction of immune suppressive molecules such as VISTA or CD39L1 (Chiu et al., 2017; Deng et al., 2019). Similarly, hypoxia inhibits the stimulatory capacity of DCs for activating T cells and instead promotes Treg homing (Winning & Fandrey, 2016). It has also been indicated that hypoxia can alter B cell function through reduced proliferation and impaired antibody class-switching (Cho et al., 2016). Targeting downstream hypoxia signaling has uncovered a promising approach for some cancer therapies and provided opportunities as a prognostic marker in tumor imaging (Huizing et al., 2019; J. Li, Zhang, Wang, & Li, 2015). Carbonic anhydrase IX (CAIX) maintains extracellular acidity under hypoxic conditions, and CAIX-targeting antibodies have been found to improve TME pH and enhance immune-mediated killing of CAIX+ tumor cells (D. K. Chang et al., 2015). Recently, anti-CAIX CAR T cells have been successful against glioblastoma in vitro and *in vivo* (Cui et al., 2019). Alternatively, targets aimed toward stimulating angiogenesis to better deliver oxygen to tissue may improve immunotherapy as well as drug delivery and/or immune cell infiltration. However, while considered an attractive target, modifying both the expression of immune checkpoints (Noman et al., 2019)

and cytotoxic T cell function, in the context of modulating hypoxia pathways may be critical.

It is important to note that hypoxia is typically replicated *in vitro* as less than or equal to 5% however this determination is controversial as it based on the standard tissue culture conditions which adopt atmospheric oxygen levels ~20% rather than physiological relevant oxygen levels. In fact, oxygenation in tissues vary but generally average around 5% while most tumors exhibit <2% oxygen (Campillo et al., 2019; McKeown, 2014). Given the central role of hypoxia in the regulation of tumor progression and immune suppression, this uncertainty surrounding the definition of hypoxia needs to be better characterized in the field. Also, because hypoxia can lead to physiological changes independent of HIF it will be important to investigate how alternative pathways may be affected and to identify the level of hypoxia in their target organ and replicate these tissue specific conditions in their experimental models.

Physiologic media as a strategy to improve the relevance of *in vitro* studies

While immune metabolism offers a plethora of opportunities to enhance cancer therapy, a barrier to translation of pre-clinical *in vitro* studies of the TME has been that tissue culture conditions under which many key findings depend have been optimized for maximal cell growth rather than to mimic *in vivo* physiology. This is particularly evident given the shared roles for some pathways in both cancer and immune cells and the context-specific effects of many metabolic pathways discussed above. Classic *in vitro* cell culture conditions rely on base media such as RPMI or DMEM, which contain excessive concentrations of nutrients that can alter the metabolism of cultured cells and lead to discrepancies in assessing metabolic mechanism for translational studies. Recently, human plasma-like media (HPLM) and similar physiological media have been developed to more closely resemble nutrient and metabolite levels found in human plasma. Such developments have begun to uncover striking differences in metabolic phenotype and drug efficacy compared to classic media. For example, the low abundance of uric acid found in RPMI resulted in an increased sensitivity of cancer cells to 5FU which overinterpreted the therapeutic effects of chemotherapies (Cantor et al., 2017). Further, the proliferation of cancer cells has been shown to depend less on mitochondrial respiration when cultured with high concentrations of pyruvate than HPLM, as indicated by their decreased sensitivity to metformin (Gui et al., 2017). Additionally, increased cystine found in classic media enhances glutamine consumption and dependency of cancer cells in culture (Muir et al., 2017). In cells cultured in traditional base media, abnormally high concentrations of arginine reverses the direction of the reaction catalyzed by the urea cycle enzyme arginosuccinate lyase, which is a metabolic feature not observed in cancer cells grown in physiological media, nor in mammary orthotopic xenografts (Ackermann & Tardito, 2019). These collective observations have been remarkable and underscore the importance of improving cell culture conditions to better reflect the TME.

The striking observations made in traditional media compared to physiologically relevant media have not been limited to cancer cells. Recently it was demonstrated that HPLM improves human T cell activation compared RPMI due to physiologic levels of calcium,

which otherwise was present at low levels in traditional RPMI. It was also reported that T cell activation in HPLM increases the expression of genes involved in several amino acid metabolism pathways that can favor inflammatory function (Leney-Greene, Boddapati, Su, Cantor, & Lenardo, 2020). This exciting discovery involving physiologic media in immune cell phenotypes offers a new appreciation for considering base media for *in vitro* conditions, particularly when assessing metabolic function. Interestingly, we have noted that while HPLM supports primary T cell activation from healthy human donors, it does not appear as effective at supporting the activation of naïve CD4+ T cells from mice (our observations). This additionally raises the concern of interpretations made from metabolic immune cell studies conducted in murine systems alone. As discussed throughout this review, it is becoming more apparent that immune cell metabolism is highly dependent on microenvironment dictated nutrient availability, further adding to the need to assess immune cell metabolism in more physiologic culture conditions in order to uncover clinically translational cancer therapies.

Refinement of media formulations and the introduction of appropriate oxygen levels and three-dimensional tissue culture systems, such as organoids or spheroid cultures will most likely reveal additional insight and improve the predictive power of *in vitro* systems. Recently, cancer-on-a-chip models have emerged as a tool to better study the heterogenous tumor microenvironment. Using microfluidic chips that contain small chambers for cell culture enable tissue mechanics that better reflect the local environment. Culturing cancer cells, macrophages and epithelial cells in a compartmentalized chips have uncovered TAMs significantly increase the ability of cancer cells to impair the endothelial barrier and that different TAM subtypes can disperse cancer cell aggregates via different mechanisms (Bai et al., 2015; Zervantonakis et al., 2012). Ultimately, *in vitro* systems aimed at better mimicking heterogeneity and nutrient availability relevant to the TME will drive further understanding of the metabolism of tumor associated immune cells and more nuanced translational approaches to cancer therapies.

Summary and Future Directions

Immunometabolism provides a wide opportunity to identify new targets to improve cancer therapies through modulation of the TME. It is clear that while studies focusing on a single metabolic pathway in cancer or immune cells are helpful to provide a better understanding of metabolism within the TME, it is unlikely that a single enzyme or transporter of a specific pathway will provide a catch-all solution. Instead, efforts that focus on combination approaches using metabolic targets coupled with chemotherapeutic or targeted interventions including immune checkpoint blockade offers the greatest potential to improve clinical efficacy. For example, metformin reduces the hypoxic state of xenograft tumors, rendering them responsive to ICB and enhancing immune cell function (Scharping, Menk, Whetstone, Zeng, & Delgoffe, 2018). In addition, phosphorylation of a serine residue on programmed cell death 1 ligand 1 (PD- L1) is AMPK-dependent, which enhances its degradation. A significant correlation was observed between the clinical response, AMPK activation and lower levels of PD- L1 expression in biopsy samples from patients with breast cancer (Cha et al., 2018). Another important consideration for TME-specific therapies is the impact of the TME on immune cell trafficking (Nicolas-Boluda & Donnadieu, 2019). Finally, effects

of host microbiome composition has been strongly implicated in the success of cancer immune therapies- specifically immune checkpoint blockades (Routy et al., 2018), creating yet another layer of complexity.

Given the effects of cell metabolism in cancer therapy efficacy, appreciation has grown for nutritional and dietary interventions. Interestingly, very low carb or ketogenic diets have boosted some anti-cancer immunotherapies (Soldati et al., 2018) whereas high-fat diets may exacerbate malignancies (Pascual et al., 2017). Similarly, caloric restriction (CR) can ameliorate the incidence and severity of certain cancers (O'Flanagan, Smith, McDonell, & Hursting, 2017). Specifically, improved outcomes from ketogenic diets, CR or intermittent fasting were associated with increased percentages of TILs and decreased Tregs (Turbitt, Demark-Wahnefried, Peterson, & Norian, 2019). The ketogenic diet depletes glucose levels, thereby lowering lactate production by glycolytic tumors. This subsequently resulted in smaller tumors, decreased MDSC frequency, and an overall improved anti-tumor immune response (Husain et al., 2013). However, manipulation of diets ultimately modulates the gut microbiome which in turn affects tumor and immune metabolism and can even play a significant role in modulating tumor responses to immunotherapy across multiple cancer types (Gopalakrishnan et al., 2018; Matson et al., 2018; Routy et al., 2018; Vetizou et al., 2015; Zheng et al., 2019). Although microbiome perturbations either indirectly by altering diet or directly by probiotics and/or fecal transplant could offer a promising strategy for a more personalized approach to immunotherapy, it still requires much caution and refinement due to the diverse functions of the gut microbiome as a whole in human health.

A new emphasis on establishing model systems that better replicate physiological conditions will help expedite our efforts to uncover clear mechanisms behind metabolic pathways and overcome the context dependent aspects of cell metabolism that are not well reflected in standard culture conditions. The majority of the immunometabolism field has drawn broad conclusions based on studies conducted in media optimized for rapid proliferation under *in vitro* culture conditions or has been limited to *in vivo* observations of murine models. Whenever possible, findings need to be challenged in multiple models, taking into account the physiological conditions of the treatment area or tumor type. This also requires documenting phenotypic changes in multiple immune cell types simultaneously in addition to cancer cells, to consider the specificity of the treatment regimen given the complexity of the TME. The tumor metabolism, immunometabolism, and immunotherapy fields have come closer in recent years, enabling a deeper understanding of these pathways and advancing combinational approaches to improve cancer therapy.

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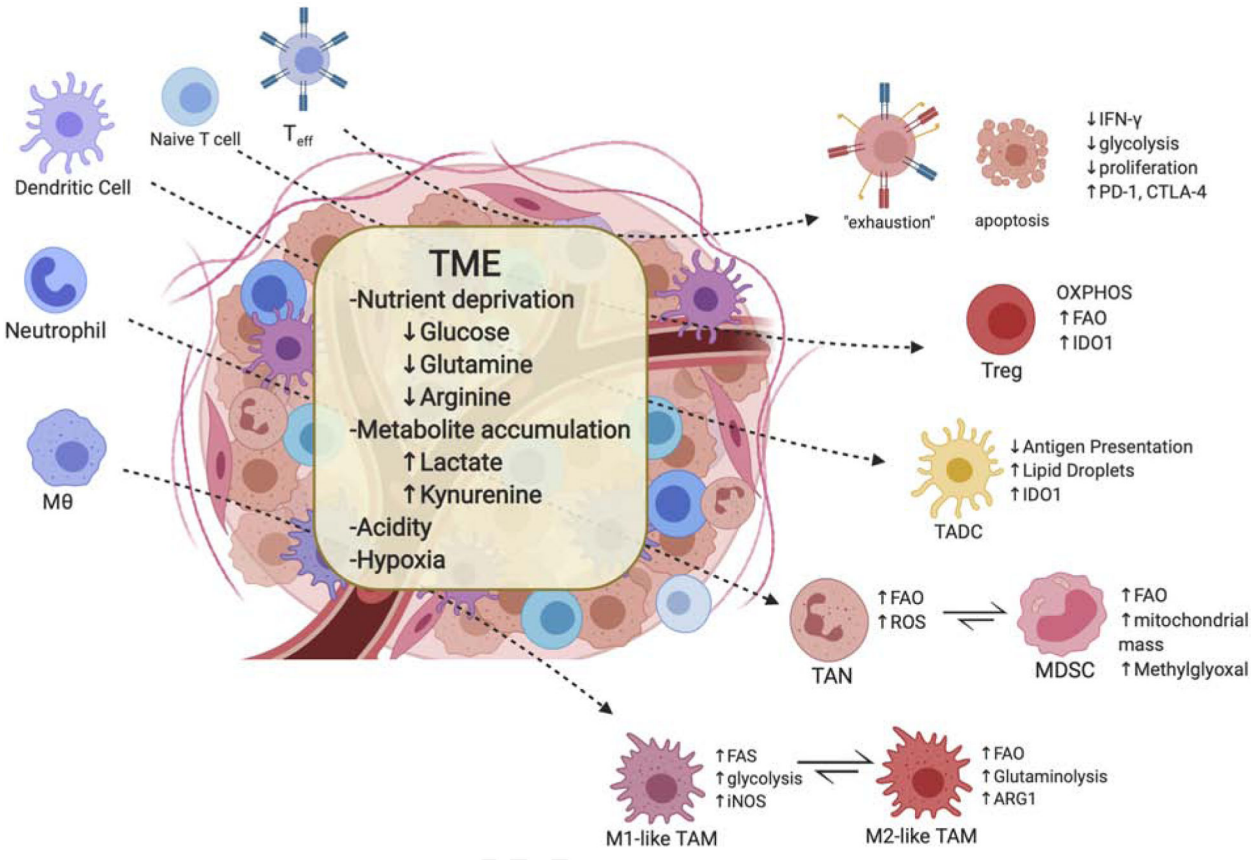

Figure 1. Tumor microenvironment and associated immune cell metabolism.

The tumor microenvironment (TME) is often characteristic of nutrient competition, low pH, limited oxygen, and accumulation of metabolites. Such conditions, in general, results in immunosuppressive or tolerogenic phenotypes of immune cells and encourages metabolism that rely more on oxidative phosphorylation and fatty acid oxidation to fulfill energy needs. Additionally, the TME accelerates T effector cell exhaustion followed by increased immune checkpoint expression on these cells. These conditions also promote differentiation and accumulation of Treg, M2-like macrophages, and MDSCs. The TME also produces unique subsets of myeloid cells known as tumor-associated dendritic cells (TADC) and tumor associated neutrophils (TAN) that have yet to fully characterized but are suggested to have suppressive or tolerant phenotypes. (MDSCs, myeloid-derived dendritic cells; Teff, effector T cell)

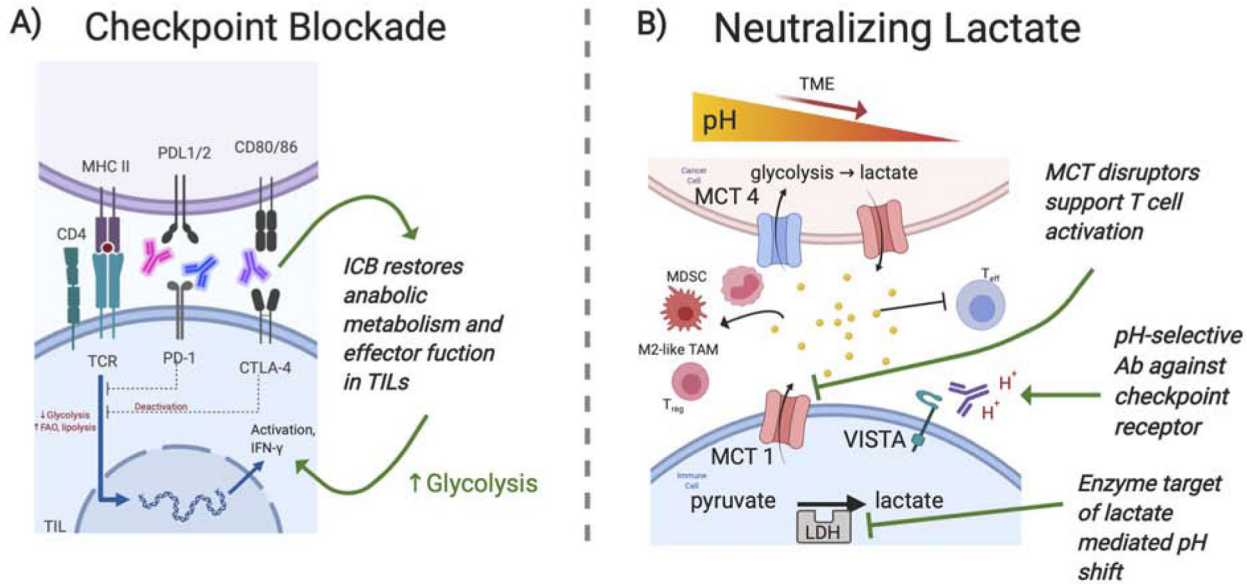

Figure 2. Potential therapeutic targets within glucose metabolism pathways.

A) Immune checkpoint blockades have emerged as a promising immune targeted strategy that has been approved clinically for a variety cancer types. Increased expression of checkpoint receptors is often the result of low glucose, acidity or lactate within the tumor microenvironment and engagement of these receptors causes an immunosuppressive phenotype characteristic of decreased glycolysis and increased FAO. Antibodies targeted against these checkpoint receptors have been successful at restoring glycolysis which in turn supports anti-tumor effector functions within immune cells. However due to the variability of immune checkpoint expression on immune cells, the most promising utilization will involve combination therapies coupling ICB with one or multiple other metabolic targets. B) Accumulation of lactate in the tumor microenvironment has been found to promote immunosuppressive immune cells through M2 macrophage polarization, MDSC infiltration, Treg survival and by inhibiting T effector functions. Strategies that decrease lactate accumulation through inhibiting lactate producing enzyme LDH, inhibiting lactate transporters, MCT1/4, or neutralizing lactic acid induced acidity have proved effective at improving antitumor immune cells. Recently utilization of acidic pH selective Abs against checkpoint receptor VISTA provides an intriguing strategy that exploits the TME to improve treatment specificity. However, targeting these pathways can be TME context and immune cell specific therefore a clear mechanism for these anticancer effects is still unclear. (ICB, Immune Checkpoint Blockades; LDH, lactate dehydrogenase; MCT, monocarboxylate transporter)

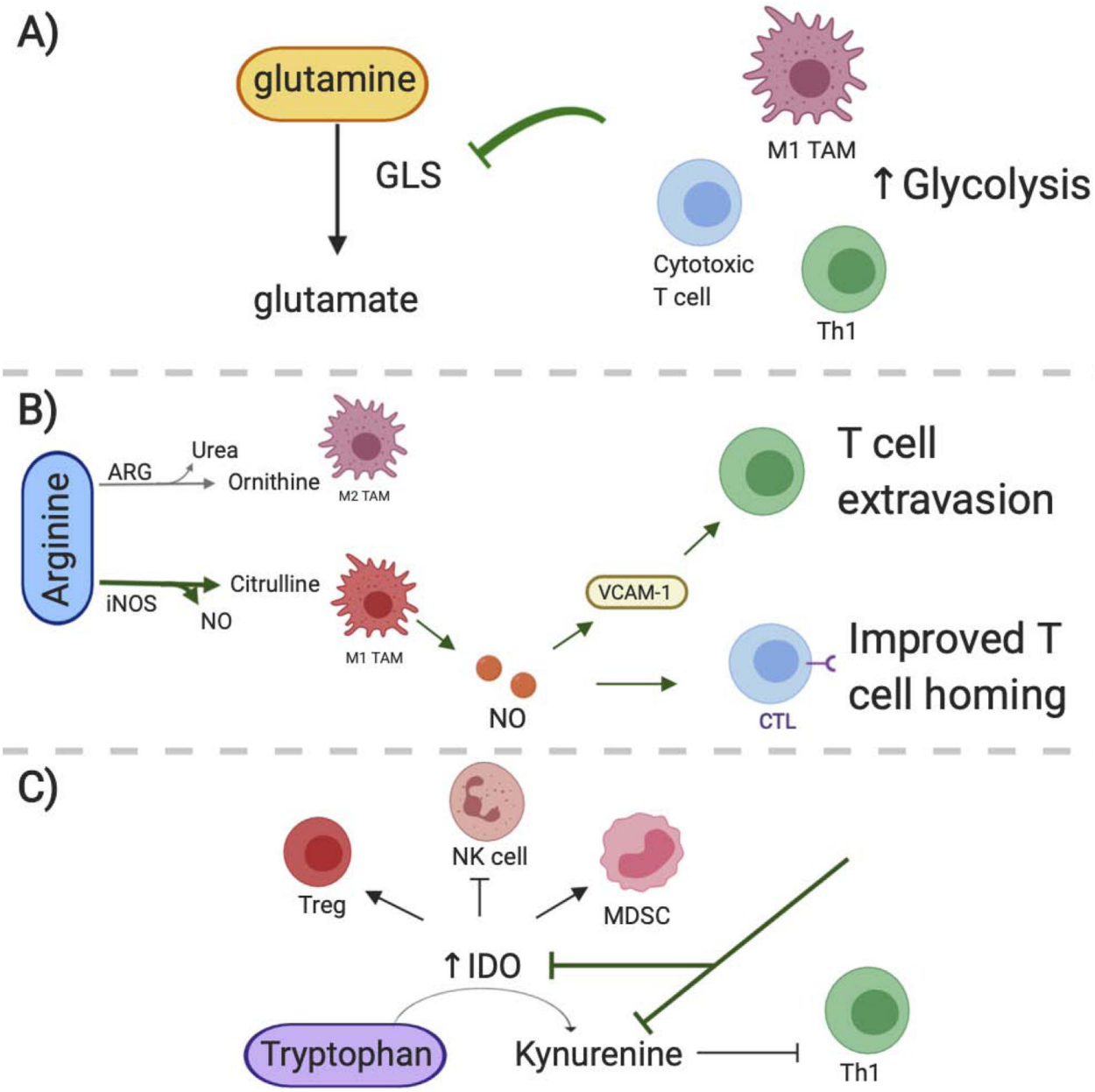

Figure 3. Promising strategies that alter amino acid metabolism within the TME.

A) Glutamine metabolism is altered as a result of the tumor microenvironment. Inhibiting glutaminolysis through blocking glutaminase (GLS) has proved to promote a proinflammatory macrophage phenotype. However specific T cell subsets can be GLS dependent or independent and thus GLS targets can have differential effects in T cell populations. B) Therapies that facilitate the metabolism of arginine through iNOS have beneficial effects in cancer therapies. Macrophages utilizing iNOS as opposed to ARG exhibit an M1 phenotype and their NO secretion promotes T cell extravasion and homing against tumors. C) Adaptive immune cell subsets, including Tregs, tolerogenic DCs and MDSCs have increased IDO expression which is the enzyme responsible for metabolizing tryptophan to kynurenine. Targeting IDO activity may suppress these adaptive immune

subsets within the tumor. Further reducing kynurenine accumulation in the microenvironment can ameliorate its immune suppressive effects against T cells. (iNOS, inducible nitric oxide synthase; ARG, arginase; IDO, indoleamine 2,3 dioxygenase)

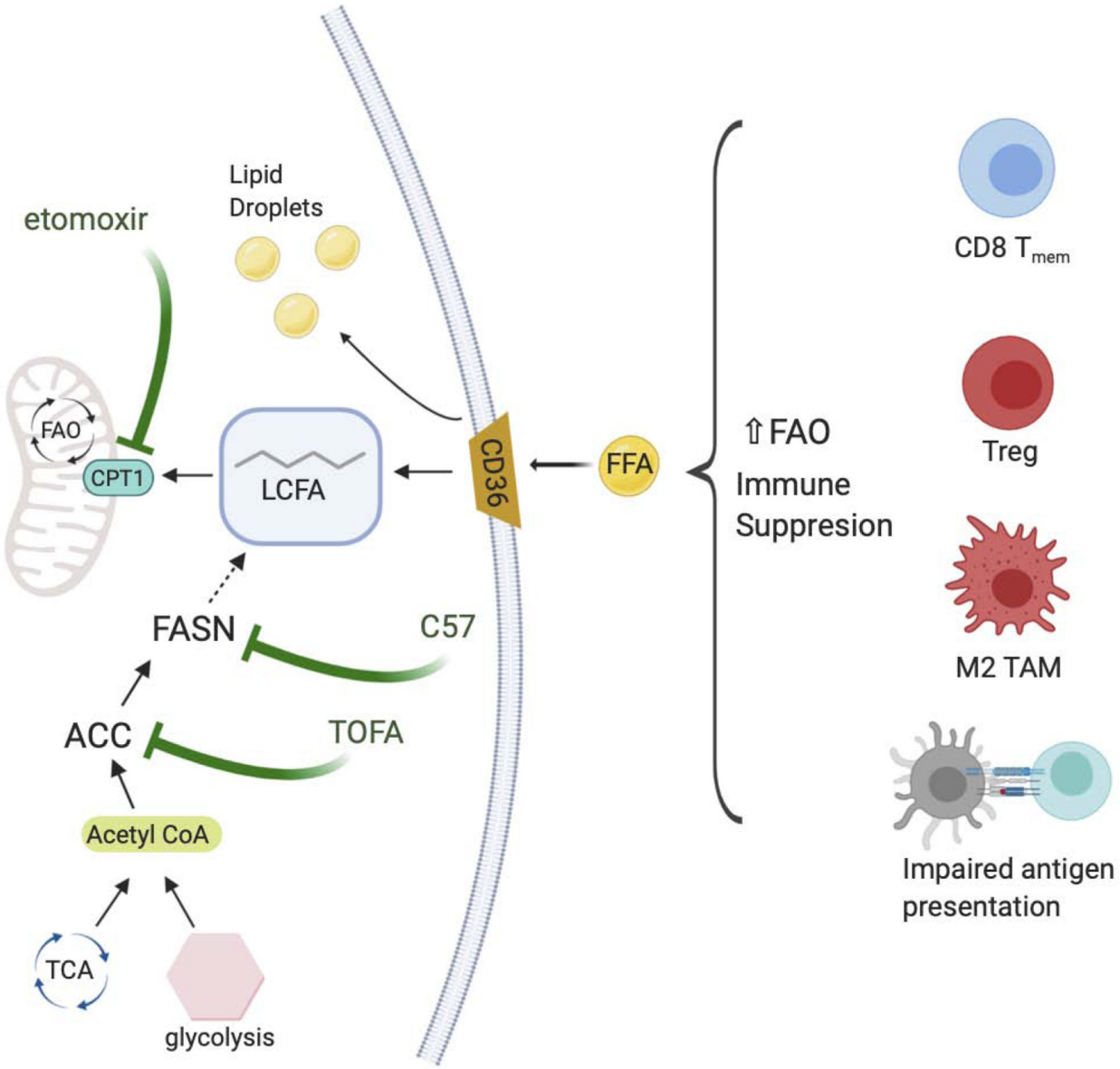

Figure 4. Manipluating fatty acid metabolism within the TME.

Increased fatty acids within a tumor microenvironment can result in accumulation of lipid droplets within immune cells or promote FAO. Immune suppressive phenotypes typically rely on FAO as a means to produce energy. Targets that inhibit CD36, the accumulation of lipid droplets, or the synthesis of FA via FASN have been found to ameliorate the FAO reliant immune suppressive metabolism. (FAO, fatty acid oxidation; FA, fatty acid; FASN, fatty acid synthase)

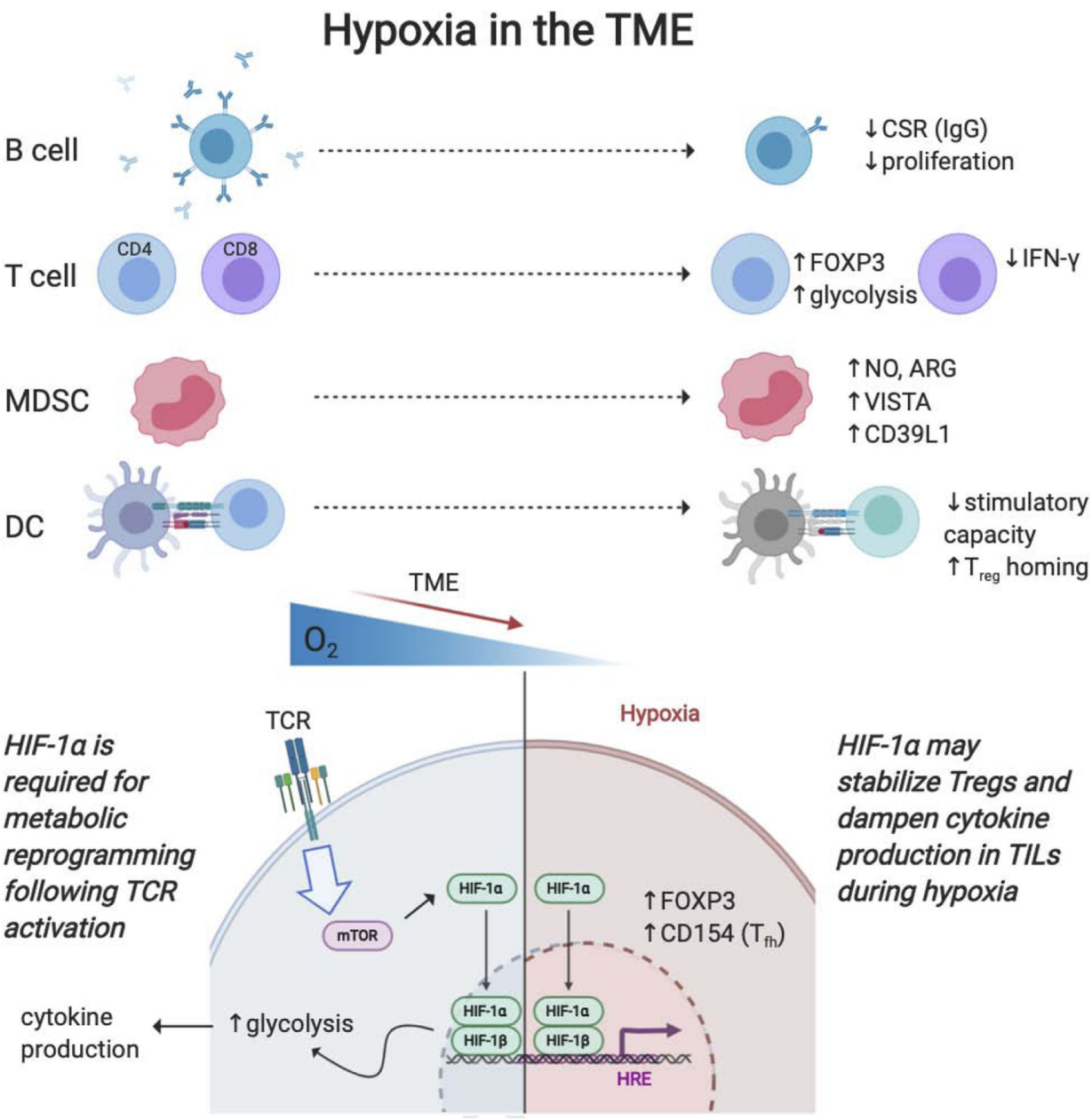

Figure 5. Immune cell response to hypoxia within the tumor microenvironment.

Due to limited vasculature of a rapidly growing tumor, areas within a tumor become hypoxic which alters immune metabolism to suppressive phenotypes. Hypoxic conditions promote T regulatory stimulation and reduce effector cytokine production. Hypoxia shifts macrophages towards an M2 like phenotype, promotes MDSC suppressive function, and reduces dendritic cell stimulatory effects. However, targeting hypoxia sensing pathway, HIF, proves to be immune cell specific and results in differential effects anti-tumor therapies. (HIF, hypoxia inducible factor)