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REVIEW ARTICLE

Metabolic reprogramming drives homeostasis and specialization of regulatory T cells in cancer

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Abstract

Transcription factor forkhead box P3 (Foxp3)+ regulatory T (Treg) cells are receiving increasing attention because this unique subset of T cells is characterized by exerting negative regulatory function of cellular immune responses. The resultant suppression of anti-tumor immunity in the tumor microenvironment (TME) is regarded as a major obstacle to immunotherapies in a plethora of cancers. Thus, an integrated understanding of the intrinsic correlation between tumors and Treg cell biology is urgently required. This review focuses on the peculiar biochemical effects of tumor metabolic environments on Tregs and how Tregs orchestrate internal metabolic switches and altered metabolic pathways and molecules to survive and function after the remodeling of homeostasis and specialization, providing new directions for immunotherapies.

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Regulatory T (Treg) cells, an inhibitory subpopulation of $CD4^+$ T lymphocytes, are indispensable for the homeostasis of the immune system and maintenance of immune tolerance in the body. They serve as a crucial barrier to anti-tumor immunity and cancer immunotherapy by directly and indirectly suppressing the proliferation, activation, and differentiation of $CD4^+$ helper T cells and $CD8^+$ cytotoxic T cells specifically against neoantigens or shared antigens in the tumor microenvironment (TME). Treg cells lack the expression of CD127 and express high levels of the α subunit of the IL-2 receptor (CD25), the key molecule for homeostasis of Tregs, and the lineage-specifying transcription factor forkhead box P3 (Foxp3), which is essential for Treg cell development and immunosuppressive function [1–3]. Notably, the molecular and functional phenotypes of Treg cells do not always remain stable but undergo a beneficial shift for Tregs to better adapt to the specific resident tissues, neighboring cells, and micro-environment [4–6]. When exposed to IL-6 with or without IL-1β and IL-23 *in vitro* or during autoimmune arthritis *in vivo*, these $Foxp3^+$ Tregs downregulate Foxp3 expression and overexpress Th17 genes, including IL-17, IL-22, IL-23R, and RORγt, reacquiring characteristics of Th17 cells, a subset of T helper cells implicated in the pathogenesis of autoimmune diseases, such as multiple sclerosis, psoriasis, and systemic lupus erythematosus (SLE) [7]. In the TME, effector Treg (eTreg) cells distinguished by $CD45RA^-FOXP3^{hi}CD127^{low}CD25^{hi}CD4^+$ constitute the major subsets that restrain antitumor adaptive immune responses through cellular and humoral mechanisms [8] and are correlated with poorer prognosis in various types of cancers [9–12]. These tumor-infiltrating eTreg cells express multiple co-inhibitory receptors on their surface, including cytotoxic T lymphocyte antigen 4 (CTLA4), programmed cell death 1 (PD1), T cell immunoreceptor with Ig and ITIM domains (TIGIT), lymphocyte activation gene 3 protein (LAG3), T cell immunoglobulin mucin receptor 3 (TIM3), and neuropilin 1 (NRP1), and secrete abundant immunosuppressive cytokines, such as IL-10, IL-35, and transforming growth factor-β (TGF-β), which downregulate the activity of both antigen-presenting cells (APCs) and effector T (Teff) cells [13].

Recent studies have highlighted the central role of metabolism in driving phenotypic and functional homeostasis and specialization of Tregs in cancer. Distinct from other T cell subtypes, Treg cells exhibit a prominent capacity to promptly adapt to the TME characterized by

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fierce nutrient competition, low pH, limited oxygen, and accumulation of metabolites, and even proliferate and exert immunosuppression in a less unaffetcted manner [14–15]. In this review, we will discuss what and how specific metabolites and metabolic pathways in the TME remodel, stabilize, specialize, and provide Treg cells surviving advantages at transcriptional, epigenetic, and cellular levels and identify the key candidate metabolic determinants that can be potentially targeted alone or in combination with current immunotherapies for better survival of patients diagnosed with carcinoma.

Tumor resident Tregs

Treg cells can be divided into two subgroups based on their originating source sites: thymus-derived Treg (tTreg) cells naturally originating from the thymus [also called natural Treg (nTreg) cells] and maturing through high-avidity interactions with MHC class II/self-peptide complexes and stimulation by IL-2 signaling; induced Treg (iTreg) cells differentiated from conventional T (Tconv) cells in the periphery [also called peripherally-derived Treg (pTreg) cells]. The iTregs can be induced *in vivo* or generated after T cell receptor (TCR) stimulation in the presence of TGF-β and IL-2 or retinoic acid *in vitro*, which frequently lack or have restricted expression of Helios and NRP1 involved in the maintenance of Treg stability and suppressive function [16–18].

The specific origins of tumor-resident Treg cells and mechanisms of Treg repertoire formation in cancer remain unclear and debated. A systematic analysis of nTreg and iTreg accumulation revealed that nTreg cells that migrated into the TME favorably recognized self-antigens, while iTreg cells preferentially recognized the same tumor-specific antigens (TSA) [19]. Recent results of T-cell receptor and single-cell transcriptome sequencing suggested that Tregs in human breast cancer may stem considerably from antigen-experienced Tconv conversion into secondary-induced Tregs through intratumoral activation [20]. This is supported by another study that explored the association between peripheral blood Treg II cells and intratumoral Treg cells [11]. However, the transcriptional analysis of Treg cells in untreated human breast carcinomas, normal mammary glands, and peripheral blood indicated that the gene expression pattern of tumor-resident Tregs resembled that of normal breast tissues than that of circulating Tregs [21]. Further comparison of the TCR repertoire of Treg cells from breast cancer and normal breast tissues in matched patients exhibited little overlap, excluding the possibility that tumor-infiltrating Tregs originate from local expansion of the tissue-resident Treg population [21], except for tumor-draining lymph nodes [22]. Moreover, tumor-associated Tregs in human bladder cancer possess a private TCR repertoire distinct from other $CD4^+$ T cells, suggesting that these immune-suppressing T cells are unlikely to be converted from other effector $CD4^+$ T cells in the TME [23]. In summary, these results revealed that tumor-resident Tregs with suppressive capacity might mainly originate from the periphery or tumor-draining lymph nodes and are subsequently recruited to the TME.

Tumor-infiltrating Treg cells directly promote tumor immune evasion, exhibiting distinct phenotypic and functional profiles, such as IL-2 consumption, secretion of granzymes and perforins, immunosuppressive cytokines (e.g., IL-10, IL-35, and TGF-β), and through the expression of multiple checkpoint inhibitory molecules, such as CTLA-4, PD-1, TIGIT, T cell immunoglobulin, mucin domain-containing protein 3 (TIM-3), and LAG-3 [24]. Moreover, they depend on the ectoenzymes CD39 and CD73 to degrade extracellular adenosine triphosphate (ATP) or adenosine diphosphate (ADP) to immune-suppressive adenosine [25].

Intriguingly, Tregs show stunning adaptive capabilities to metabolic changes in the TME by regulating several signaling pathways, among which the PI3K/Akt signaling pathway plays a central role. Once activated by upstream TCR and IL-2 signaling in Treg cells, PI3K/Akt signaling directly controls the phosphorylation of Foxo (Foxo1 or Foxo3a) transcription factors and blocks their nuclear translocation [26–27]. When Akt is hypoactivated, nuclear Foxo abundance is correspondingly elevated on the promoter regions of Foxp3, giving rise to Foxp3 expression and stability of tTregs [28–30], This process can be mediated by Sema4a in a PTEN-dependent manner [31]. The mTOR signaling is the upstream of metabolic reprogramming. Furthermore, Akt can affect the mTOR signaling including mTORC1and mTORC2, is affected by Akt [32]. Akt phosphorylates TSC2 to relieve TSC complex inhibition of mTORC1, which has been reported to be essential for Foxp3 expression at low doses [33]. This is in agreement with previous observations that co-stimulation with TCR and IL-2 *in vitro* could reverse the anergic state of freshly isolated Treg cells by re-activating the Akt-mTOR signaling inhibited by PTEN [34].

Metabolic profiles in the TME

Tumor cells are characterized by their unparalleled competence in the uptake of oxygen and various other nutrients and outstanding resilience to local environmental changes through metabolic reprogramming to sustain proliferative signaling, evade growth suppressors, resist cell death, enable replicative immortality, induce angiogenesis, and activate invasion and metastasis [35]. In 2016, Pavlova and colleagues concluded that six tumor-associated metabolic modifications occur in the TME: (1) deregulation of glucose and amino acid metabolism, (2) altered nutrient uptake, (3) utilization of intermediates from the citric acid cycle (TCA cycle)/glycolysis for

the biosynthesis of nicotinamide adenine dinucleotide phosphate (NADPH), (4) increased nitrogen requirement, (5) variations in the regulation of metabolite-dependent gene expression, and (6) interactions between metabolic pathways within the TME [36]. Due to the unlimited consumption of these nutrients, the tumor microenvironment always presents with a hypoxic, acidic, and glucose-low state, which is unsuitable for the survival of large numbers of normal cells. In particular, tumor cells prefer aerobic glycolysis for glucose metabolism when compared with normal cells, even under oxygen-rich conditions, which is called the Warburg effect [37]. Glycolysis is also promoted by high expression levels of hypoxia-inducible factor (HIF) induced in hypoxia, and the final metabolic product lactic acid, generated in this process, is exported through monocarboxylate transporter (MCT) on the cell membrane to the TME together with the carbonic acid formed during oxidative phosphorylation, contributing to the formation of low pH environments [38–40]. In addition, de novo synthesis of fatty acids in cancer cells is elevated, and the limited availability of free fatty acids can control the proliferation of these cells [41–42]. Glutamine metabolism is also enhanced [43], but the role of the metabolism of other amino acid vary among tumors owing to their vast heterogeneity [44–46]. Together, these metabolic changes occurring in the TME are mainly mediated by genetic variations, epigenetic modifications, and metabolic reprogramming in tumor cells, facilitating their proliferation, metastasis, and invasion. Notably, these metabolic changes also force chain changes in other cells infiltrating the TME, subsequently causing the re-construction of immune responses favoring cancers, strengthening the activities of cells inhibiting immunity, such as Treg and Macrophage 2.

Less glucose, more stability

Unlike Teff cells, which show significant dependence on glucose for survival, proliferation, differentiation, and function, Treg cells exhibit striking plasticity and acclimation capacity when confronted with a glucose switch [47], that is, uptake glucose more efficiently than Teff cells when needed [48] and remain functionally and phenotypically stable in glucose-restricted environments. Glucose is used for energy production in Tregs via oxidative phosphorylation (OXPHOS) and glycolysis, and its availability in the specific resident environment directly determines the dominant metabolic pathway [49]. Treg cells exhibit significantly higher levels of glycolysis than Teff cells in the glucose-poor TME [50], thus inducing cellular senescence and suppression of responder T cells through crosstalk, which can be reversed by activating TLR8 signaling-mediated reprogramming of glucose metabolism [51]. Compelling evidence has shown that glycolysis and OXPHOS directly and indirectly control Treg activity through transcriptional and epigenetic modulations and involvement in various critical intracellular signaling pathways that determine the fate of tumor-infiltrating immune cells [52–57]. Glycolytic activity in Tregs varies considerably among resident tissues, Treg populations, and disease models depending on the expression of upstream enzymes (e.g., phosphofructokinase-1, glycogen phosphorylase inhibitor) and glucose transporters [e.g., GLUT1(glucose transporter 1) and GLUT3 (glucose transporter 3)][51, 55, 58–60]. The migratory capacity to secondary lymphoid organs and proliferating activities both rely on mTORC2-mediated upregulation of glycolysis [61–62], favoring Treg survival in a hostile environment. However, when a certain concentration is exceeded, glucose impairs the suppressive function and stability of Tregs [63]. A recent study illustrated a direct relationship between tumor glycolysis and intratumoral Treg cell stability by comparing their phenotypes and functions in high and low glycolytic TME and concluded that Tregs with greater availability of glucose were less stable [64]. The deprivation of glucose through the deficiency of GLUT1 mostly mediates glucose uptake in Tregs. While, it favors iTreg cell differentiation from Tconv cells by driving Foxp3 expression [65]. In addition, it retains stronger suppression function ex vivo in glycolysis-defective tumors compared to control Treg cells [64]. Despite conflicting results on Glut1 expression probably resulting from heterogeneous tissues and Treg populations, this glucose transporter is deleterious to the stability and suppressive capacity of Tregs, particularly in the TME [55, 60, 65–66]. Notably, glucose uptake through Glut1 indispensably guarantees the expansion and proliferation of Tregs [64], suggesting that this metabolite exerts different effects and is important at different stages of Treg growth and development.

How does glucose drive the regulation of Treg function and homeostasis?

Characterized as a suppressive marker of Tregs, Foxp3 acts as a direct functioning target and a critical switch point mediating the interaction between epigenetic modifications and metabolic modulations. Foxp3 suppresses c-Myc expression and glycolysis, enhances oxidative phosphorylation, and increases nicotinamide adenine dinucleotide oxidation [67], whereas the deficiency of this transcription factor results in augmented aerobic glycolysis and oxidative phosphorylation [52]. However, these Treg cells could restore their suppressive function caused by Foxp3 deficiency through the inhibition of rapamycin-insensitive companion of mTOR (RICTOR) or mTORC2 depletion [52]. Mammalian target of rapamycin (mTOR), consisting of complexes I (mTORC1) and II (mTORC2), coordinates the transcriptional programs and cellular metabolism of Tregs, thereby integrating

metabolite availability and growth factor signaling. The discrepancy between the *in vitro* anergic state of Treg cells and their proliferative capability *in vivo* partly lies in activating mTOR signaling *in vivo* [68]. Specifically, PTEN deficiency upregulates mTORC2 signaling, thus increasing glycolytic activities and reducing the stability and suppressive functions of Tregs [69]. Similarly, PI3K-Akt-mTORC1 signaling induced by Toll-like receptor (TLR) signals also increased glycolysis and impaired the suppressive capacity of Tregs and is opposed by Foxp3/Foxo1 to diminish glycolysis and anabolic metabolism [28, 50, 55]. Interestingly, the elevation of PI3K mediated mTOR signaling has minimal effects on tTregs but dramatically increases glycolysis and reduces the expression of Foxp3 in normally oxidative iTregs [58], accompanied by di- and trimethylation of lysine 4 of histone H3 (H3K4me2 and -3) near the Foxp3 transcription start site and within the 5` untranslated region [33]. In agreement with this, mTOR signaling was also reported to be a crucial downstream signal upon TCR activation for regulating T cell de novo differentiation into Tregs, associated with decreased signal transducer and activator of transcription factor activation and failure to upregulate lineage-specific transcription factors [70].

Instead of glycolysis, OXPHOS appears to be the key fuel source for driving the functions of Tregs and is directly regulated by Foxp3 [71]. In addition, Treg suppressive function was reported to be impaired through Treg-specific deletion of mitochondrial complex III in adult mice, with no impact on the expression levels of Foxp3 or the number of FoxP3+ Tregs [72]. In contrast, blocking OXPHOS with oligomycin reduces FOXP3 expression and IL-10 production in Treg cells [64], in agreement with previous findings [66, 72], whereas forcing glycolysis in Treg cells makes them more susceptible to loss of stability. Dysfunctional Tregs in mice lacking the metabolic sensor Lkb1 led to disrupted mitochondrial metabolism and subsequent lethal autoimmunity, similarly underlying the essential role of OXPHOS in their suppressive function [73–74]. The genetic ablation of Tfam (mitochondrial transcription factor A, essential for mitochondrial respiration and mitochondrial DNA replication, transcription, and packaging) in Tregs impairs Treg maintenance in non-lymphoid tissues and in tumors by enhancing methylation in the Treg cell specific demethylation region of the Foxp3 locus [75], revealing potential interactions between Foxp3 and OXPHOS. Another linking molecule, the nuclear factor of activated T cells (NFAT), binds to the non-coding sequence 2 (CNS2) of the enhancer upstream of the Foxp3 gene and promotes its expression [76]; it is activated by metabolic reactive oxygen species (mROS) produced during OXPHOS [77].

The role of fatty acid oxidation (FAO)

FAO (producing acetyl-CoA, which enters the mitochondrial tricarboxylic acid (TCA) cycle) and glycolysis both provide substrates for the OXPHOS process to maintain suppressive functions of Tregs [60]. Under inflammatory conditions, regulatory T cells preferably rely on exogenous fatty acids (primarily oleic acid) rather than fatty acids endogenously generated through acetyl-CoA carboxylase 1 (ACC1)-mediated de novo fatty acid synthesis for FAO [78–79]. In the TME, although the relative abundance of free fatty acids across various cancers is still debated, men could confirm that the high levels of free fatty acid in some cancers (e.g., in RHOA mutated gastric cancer) confer Tregs surviving and proliferative advantages towards Teffs [80], inferring the vital roles of exogenous fatty acids for Tregs and the existing lipid metabolic reprogramming. However, endogenous fatty acids are also indispensable for the proliferation, stability, and specialization of intratumoral Tregs [60, 81–82]. Intratumoral Tregs upregulate the expression of fatty acid transporters CD36 and SLC27A1 and activate PPAR-β pathways to increase lipid uptake and decrease glucose oxidation, orchestrating the survival and suppressive functions of intratumoral T cells [81, 83]. In the colorectal cancer (CRC) TME, accumulation of OX40+ Tregs in the visceral adipose tissue (VAT) of obese CRC patients suggested that these Tregs might migrate from their 'transit stations' full of polyunsaturated fatty acids into the TME via chemotaxis [84]. Mechanistically, lipid uptake and oxidation affect the homeostasis and function of Tregs through direct and indirect pathways [85-88]. The pharmacological inhibition of FAO with etomoxir targeting carnitine palmitoyltransferase 1a (CPT1a) and using an shRNA approach to reduce CPT1a levels in Tregs both resulted in the abrogation of FoxP3 expression (the determining factor of Treg homeostasis and function) and promoted differentiation and proliferation of Tregs rather than Teffs [85]. The elevated levels of Foxp3 in turn upregulated components of all the electron transport complexes and enhanced ATP generation through FAO-fueled OXPHOS metabolism, forming a positive feedback loop between FAO and Treg-suppressive function [71, 79]. Additional evidence supporting the indispensable roles of FAO in Tregs indicates that dysregulated mitochondrial metabolism is responsible for the impaired suppressive function of Tregs after inhibition of lipid uptake by targeting FABP5, the key regulator of lipid uptake and intracellular trafficking [88]. It is interesting to note that FABP-mediated lipid metabolism in plasmacytoid DCs (pDCs) also supports the appropriate generation of regulatory T cells (Tregs) in the TME [89]. Moreover, AMPK signaling inhibition was reported to facilitate fatty acid entry into the mitochondria, thus promoting OXPHOS and enforcing Treg function and proliferation

[56], in agreement with previous observations that iTreg cells have high levels of activated AMPK and FAO [66]. In contrast, Tregs also rely on the activation of transcription factor SREBP-dependent de novo lipid biosynthesis to facilitate subsequent TCR-induced maturation and maintain the expression of PD-1 [82,89]. Notably, short-chain rather than long-chain fatty acids could help stabilize the expression of Foxp3 [87], strengthen mitochondrial oxidative capabilities [90], promote differentiation of Tregs [91], and limit anti-CTLA4 therapies [92], probably by downregulating the expression of histone deacetylases, such as HDAC6 and HDAC9 [87], which were reported to destabilize Foxp3 protein [93]. However, one must concede that the precise mechanisms by which FAO reprograms the functions and homeostasis of Tregs still require further investigation.

Amino acids

Amino acids are used as substrates in multiple metabolic pathways, and some of them or their derivatives, including glutamic acid, tryptophan, kynurenine, arginine, and isoleucine, have been found to play decisive roles in the differentiation, proliferation, and stabilization of Tregs [94–98]. Glutamine not only fuels the TCA cycle to provide essential energy for cancer growth [43] but also facilitates maintenance of the intracellular glutathione (a tripeptide of cysteine, glutamate, and glycine) pool through cysteine-glutamate transport, thus preventing reactive oxygen species (ROS) accumulation and counteracting oxidative stress [99]. Thus, intratumoral Tregs have given up competence for this metabolite and adapted to survive and function in glutamine-low microenvironment, deprivation of glutamine in the media, or addition of the glutaminase inhibitor 6-diazo-5-oxo-l-norleucine (DON) oppositely increased Foxp3 expression and contributed to the suppression of these T cells [100–101]. Notably, as the tumor cells consumed glutamine and exported glutamate in exchange for cystine, the resulting high-glutamate microenvironment also favors the accumulation and function of Tregs, and VEGF blockade could further increase glutamate levels, revealing potential mechanisms contributing to failures of VEGF blockade therapies in glioblastoma [102].

Indoleamine 2,3-dioxygenase (IDO), an enzyme that catabolizes the amino acid tryptophan and mediates its conversion to kynurenine, has also been shown to be positively correlated with the differentiation and proliferation of Tregs [103–104]. Resting $CD4^+CD25+Foxp3^+$ Tregs can be directly activated to exert potent suppressor activity by a small population of pDCs expressing IDO [105]. Various types of tumor cells also highly express IDO, thus elevating the concentration of kynurenine in the TME [106–107], which has been reported to drive the generation of Tregs and tolerogenic myeloid cells by interacting with the ligand-activated transcription factor aryl hydrocarbon receptor (AHR) [94]. Blockade of AHR signaling could reverse Treg–macrophage interplay-dependent immunosuppression and delay the progression of IDO-overexpressing tumors with (better efficacy) or without the combination of PD-1 therapies [94]. Moreover, IDO also functions in Tregs by inhibiting the mTOR/Akt axis and upregulating FoxO3 upon activation, partly accompanied by upregulation of PD-1 and subsequent activation of PTEN, which finally blocks phosphorylation of Akt on its other activating site in a so-called positive-feedback loop to favor Treg differentiation/function/stability [108]. Other amino acids, such as isoleucine [98], leucine [109], and arginine [109], were all shown to be essential for sustaining Treg proliferation; the latter two amino acids probably act as key inducers activating mTORC1 signaling in Tregs to license Treg function [109].

Significantly, multiple solute carrier (SLC) molecules mediating amino acid transport across the plasma membrane have been identified to directly control Treg activity and are involved in the regulation of immune responses in the tumor microenvironment [110]. SlC3A2-deficient Treg cells show impaired branched-chain amino acid (BCAA)-induced activation of the mTORC1 pathway and an altered metabolic state, followed by decreased replication *in vivo* and low cell density [98]. Knockdown or pharmacological inhibition of the cystine/glutamate antiporter SLC7A11 proved to be deleterious to proliferation and function rather than the viability of TCR-stimulated human Tregs through the leptin-mTOR axis [111]. However, there is also evidence that the deletion of amino acid transporters ASCT2 and SLC7A5, transporters of glutamine and leucine, has no impact on Treg differentiation [112–113].

Impacts of other metabolic factors on Tregs in the TME

Hypoxia

It has been earlier observed that the suppressing capability and homeostasis of nTregs were enhanced under simulated hypoxic conditions [114]. The elevated expression of the intratumoral chemokine CCL-28 in the hypoxic TME facilitated the recruitment of Tregs [115]. In response to hypoxic microenvironments, hypoxia-inducible factor 1α (HIF-1α) and HIF-2α binding to hypoxia response elements (HREs) is increased [116], acting as the central node to coordinate the hypoxic regulation of Treg activity. HIF-1α was found to promote glycolytic-driven migration of Tregs by directing glucose away from mitochondria, leaving Tregs dependent on fatty acids for mitochondrial metabolism [83]. In contrast, crosstalk can be found between HIF-2α and HIF-1α. HIF-2α represses HIF-1α expression. HIF-1α is upregulated in HIF-2α-KO (Knockout) Treg cells [116]. Foxp3-conditional KO of

HIF-2α in mice led to restricted growth of MC38 colon adenocarcinoma and metastases of B16F10 melanoma, revealing its distinct effects on strengthening Treg-mediated suppression of antitumor immune responses [116]. Interestingly, the roles of HIF-1α in regulating the suppression and homeostasis of Tregs are diametrically opposite in the TME compared to those in inflammatory environments [117–118]. Depletion of HIF-1α in Treg cells inhibits downstream glucose transport and glycolysis and restores Foxp3 stability *in vivo* or *ex vivo*, thus increasing mitochondrial metabolism, such as oxidative phosphorylation, and enhancing their suppressive capacity [38, 83, 117, 119]. However, it remains doubtful whether Tregs that restore high consumption of oxygen in hypoxic environments could adapt to such drastic energetic switches and sustain prolonged survival. HIF-1α KO mice bearing GL-261 brain tumors showed increased survival compared to WT mice [61, 83], suggesting a delicate balance between survival and function in plastic Tregs.

Acidity

The major source of intra-tumoral acidification arises from the large amounts of lactate produced by tumor cells through anaerobic, oxygen-limited metabolism pathways. Typically, lactate has long been described as a waste metabolite that directly enhances tumor cell motility and assists tumor immune escape by inducing apoptosis of naïve T cells and ultimately inhibiting antitumor immunity [120]. However, recent studies have revealed the significant role of lactic acid as a primary circulating TCA substrate in tumors and other cells [121–122]. Conventional Teff cells sustain glycolytic flux by converting pyruvate into lactate and utilizing the consequently generated NAD nicotinamide adenine dinucleotide. Tregs, as previously mentioned, nevertheless, prefer to maintain the NADH/NAD+ ratio by oxidizing exogenous lactate and endogenous pyruvate in the mitochondria instead of converting pyruvate to lactic acid because they do not rely on high-rate glycolysis to fuel cellular activities [67]. Therefore, Tconv cells, rather than Tregs, struggle to proliferate and function in the presence of extracellular lactic acid or sodium lactate because they are unable to excrete the lactate produced due to loss of gradient [67]. Although Tregs display the ability to uptake exogenous lactic acid, the results *in vitro* by depleting MCT1-a, Although Tregs display the ability to uptake exogenous lactic acid, the results from an in vitro study indicated that the MCT1-a (Monocarboxylate transporter1-a) may not be indispensable for Treg function [63]. Combined with previous observations that lactate drove naive T cell polarization and increased the frequencies of iTregs in the TME in a TGF-β-dependent manner [123] but did not affect Treg function and stability *in vitro* after manual addition of lactate [64], and that lactate enhanced tryptophan metabolism and kynurenine production by pDCs [96], we hypothesize that lactate indirectly helps maintain the relative advantages of Tregs by suppressing Tconv cells and stimulating Treg-associated cells and pathways. Moreover, lactic acid also contributes to tumor growth by inducing the expression of vascular endothelial growth factor and M2-like polarization of tumor-associated macrophages in a HIF-1α dependent way [124]. It would be interesting to investigate the deeper links between lactate, Tregs, and other immune cells.

Concluding remarks

Despite the plethora of metabolic threats, such as nutrient restriction, acidity, and oxidative stress, imposed by the TME on infiltrating immune cells, Tregs display strikingly adaptive competencies to survive, proliferate, and function. In this review, we provide a comprehensive understanding of how Tregs deal with these metabolic stresses based on recent publications. As described above, Treg cells show broad heterogeneity in glucose and lipid metabolism within various contextual features, which may not be limited to a certain pathway. For example, conflicting results have been observed regarding the impact of glycolysis on the proliferation and suppressive function of Treg cells [52–57]. Further research utilizing frontier technologies is needed to investigate the epigenetic and molecular signaling mechanisms driven by metabolic reprogramming, which have been demonstrated to affect the differentiation of Tregs and their suppressive and migratory properties. Considering the wide and profound involvement of metabolic reprogramming in TME, targeting metabolism is viewed as a promising therapeutic approach for cancer therapy. One can envision that these approaches may synergize with current effective anti-tumor strategies.

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