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Metabolic reprogramming and tumor immunity under hypoxic microenvironment

Ronghui Yan[1], Linchong Sun[1,2] and Huafeng Zhang[1]

Cancer cells are frequently surrounded by hypoxic microenvironment and, to survive, they have evolved multiple adaptations. One of the hallmark adaptations for cancer cells is the rewired metabolism, in which hypoxia plays important roles. Besides rewired metabolism in cancer cells, much progresses has emerged in hypoxia-regulated immune cells and immune responses as well. Here, we will review the recent progress in the field of rewired cancer metabolism and tumor immunity regulated by hypoxic microenvironment.

Addresses
[1] Hefei National Laboratory for Physical Sciences at Microscale, The CAS Key Laboratory of Innate Immunity and Chronic Disease, School of Life Sciences, University of Science and Technology of China, Hefei, 230027, China
[2] Laboratory of Cancer and Stem Cell Metabolism, School of Medicine, Institutes for Life Sciences, South China University of Technology, Guangzhou, 510006, China

Corresponding author: Zhang, Huafeng (hzhang22@ustc.edu.cn)

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Introduction

Life has started to utilize oxygen since ~1.5 billion years ago with the emergency of eukaryotic organisms containing mitochondria, in which oxygen (O_2) serves as a key substrate for mitochondrial ATP production through the respiratory chain [1]. However, in solid tumors, oxygen delivery to the respiring neoplastic and stromal cells is frequently decreased or even abolished by severe structural abnormalities of tumor microvessels and damaged microcirculation [2]. Therefore, cancer cells in solid tumors usually suffer from hypoxic stress. To adapt to this micro-environmental hypoxic stress, cancer cells develop O_2 sensing pathways. Hypoxia inducible factors (HIFs), especially, HIF-1 and HIF-2, are O_2 responding proteins and have elevated expression in multiple cancers containing hypoxic regions. HIF-1 and HIF-2 transcriptionally regulate the expression of hundreds of genes which affect the occurrence and development of tumors through many ways, including genetic instability, epithelial–mesenchymal transition, invasion and metastasis, vascularization, pH regulation, metabolic reprogramming, and immune evasion [3–7].

Metabolic reprogramming and tumor immunity

Since the aerobic glycolysis, the so called 'Warburg Effect', in cancer cells was discovered about one century ago, cancer cell metabolism has become a hot research field in the past few decades. In view of those fundamental discoveries, tumorigenesis undoubtedly depends on metabolic reprogramming to acquire necessary nutrients from the frequently nutrient-poor microenvironment and then utilize these nutrients to maintain cancer cell viability and build new biomass for cancer cells to keep proliferating. Cancer-related alterations of intracellular and extracellular metabolites have profound effects on promoting cancer cell proliferation as well as remodeling the tumor microenvironment, in which various immune cells reside. In contrast, establishing why some cancers progress while others do not is a longstanding challenge in immunology. Hypoxia and expression of HIF-1α and HIF-2α are characteristic features of most solid tumors, and it has also been reported that HIFs induce a number of host immune responses [8]. Therefore, exploration on hypoxia associated cancer immunology has attracted more and more attention in recent years. Hence, metabolic reprogramming and immune disorder have been viewed as two emerging hallmarks of cancer. Here, we will review the rewired cancer metabolism and tumor immunity regulated by hypoxic microenvironment in solid tumors.

Metabolic reprogramming of cancer cells under hypoxic microenvironment

The early observation of cancer cell-specific metabolism was described by Otto Warburg in 1920s who discovered that, even in the presence of ambient oxygen, cancer cells prefer to generate ATP via glycolysis rather than oxidative phosphorylation (OXPHOS), in which glucose enters into the TCA cycle in mitochondria. This phenomenon is the so-called 'Warburg Effect'. Cancer cells frequently suffer from hypoxic stress and as a response, the expression of HIFs is turned on to rewire cancer cell metabolism for survival. HIFs directly facilitate the expression of glycolytic enzymes to enhance 'Warburg Effect' in cancer cells at transcriptional level, while decrease the activity of mitochondria to avoid apoptotic cell death caused by increased mitochondrial ROS [9,10]. In order to satisfy the tumor cells' large demand for fatty acids, hypoxia is

also involved in promoting lipogenesis via reductive glutamine metabolism and suppresses fatty acid β-oxidation by inhibiting fatty acid catabolic enzymes MCAD and LCAD expression [11,12].

Recently, a series of new metabolic adaptations to hypoxia have been uncovered. As is known, cancer cells are often surrounded by nutrient-poor and oxygen-poor conditions, thus, they need to develop additional nutrition sources to bypass these limitations. It has been reported that cancer cells consume acetate and ketone bodies to fuel cancer cell growth and metastases [13–15]. Recent studies showed that hypoxia produced lactate also served as carbon source for cancer cells. In human non-small-cell lung cancers, lactate was absorbed avidly by MCT1 and subsequently transformed into pyruvate to fuel the TCA cycle and facilitate cancer progression [16,17]. Moreover, hypoxia-induced lactate results in intracellular acidification. Walton *et al.* found that hypoxia-induced intracellular acidification promotes translocation of lysosomes from perinuclear to peripheral regions, resulting in lysosome separation from perinuclear protein RHEB. Since lysosomal RHEB is essential for the activation of lysosome-bound mTOR, therefore, lysosome separation from RHEB leads to suppressed mTOR activation and downstream mTORC1 signaling including translation related protein phosphorylation. Maintaining of circadian clock relies on rhythmic expression of genes and hypoxia-induced acidification collapse the circadian clock by altering clock genes' translation as a result of mTORC1 inhibition [18••].

New progress has also emerged in metabolic reprogramming of amino acids in tumors. In MYC-transformed cells, hypoxia induces mitochondrial serine hydroxymethyltransferase (SHMT2) expression to catabolize serine, resulting in NADPH production to relieve cellular oxidative stress [19]. Garcia-Bermudez *et al.* assessed the proliferation of a collection of cancer cells following inhibition of the mitochondrial electron transport chain (ETC). Along with metabolomic analysis, they uncovered that sensitivity to ETC inhibition varied across cell lines, specifically, aspartate dropped remarkably in ETC inhibition-sensitive cancer cells but not in resistant cells. Since the synthesis of aspartate is limited in ETC-impaired cancer cells and aspartate has poor cell permeability, they hypothesized that different intracellular aspartate levels in these two types of cancer cells resulted from diverse aspartate transporting abilities. Indeed, they found that overexpression of SLC1A3, an aspartate transporter, attenuated the sensitivity of cells to ETC inhibition. In this study, aspartate was found as a limiting metabolite for cancer cell proliferation under hypoxia and ETC inhibition via regulating nucleotide production [20••]. Moreover, Sullivan *et al.* raised that aspartate suppression could be effective for anti-cancer therapy [21]. Interestingly, Kanarek *et al.* recently reported dietary supplementation of histidine will improve methotrexate chemotherapeutic efficacy, because histidine breakdown product formiminoglutamic acid (FIGLU) would exhaust tetrahydrofolate (THF) to prevent nucleotide synthesis in methotrexate-treated cells, in which the THF pool is already limiting [22]. Thus, further amino acids metabolism in cancer cells as well as their therapeutic potentials remain to be explored.

In contrast, acetate also fuels cancer cells. Recently, Gao *et al.* found that acetate recovers hypoxia-suppressed histone acetylation of H3K9, H3K27, and H3K56, which are important for gene transcription. Lipogenic genes ACACA and FASN are predominately activated by acetate supplementation under hypoxia. Mechanistically, both ACSS1 and ACSS2 are involved in this acetate-induced lipogenic gene expression by converting acetate to acetyl-CoA, thereby enhancing epigenetic acetylation modification [23•]. Thus, acetate promotes cellular lipogenesis not only by providing raw materials for *de novo* lipid synthesis but also promoting lipogenic gene expression via epigenetic regulation. This research extends the role of acetate to epigenetic modification under hypoxia; by then, whether other metabolites function similarly or not remains largely unknown. However, hypoxia regulates epigenetic inheritance in far more ways than this. For example, hypermethylation of the promoters of tumor suppressor genes is reported to impede transcription of these genes inhibiting cell growth. Thienpont *et al.* found that the activity of oxygen-dependent 10–11 translocation (TET) enzymes, which catalyze DNA demethylation, is directly reduced by oxygen shortage under hypoxia. Downregulated TET activity resulted in markedly enhanced methylation of the promoters of tumor suppressor genes and decreased their expression at mRNA level. Mechanistically, similar as prolyl-hydroxylase domain proteins (PHDs), TET enzymes are Fe^{2+} and α-ketoglutarate dependent dioxygenases which are oxygen-sensitive, thus the TET enzyme activity is directly regulated by hypoxia [24••]. Furthermore, N6-methyladenosine (m6A) modification of mRNA also plays critical roles in tumorigenesis. Breast cancer cells exposed to hypoxia are with a higher expression of AlkB homolog 5 (ALKBH5), an m6A demethylase, which demethylated NANOG mRNA at an m6A residue in the 3′-UTR, leading to enhanced NANOG mRNA. Increased NANOG expression programs breast cancer cell into breast cancer stem cell (BCSC) [25]. Taken together, these researches highlight that hypoxia regulates tumors both at transcriptional and epigenetic levels.

Moreover, recent studies have shown that hypoxia regulates protein function by altering its subcellular translocation. For instance, hypoxia promotes nuclear high mobility group box 1 (HMGB1) translocating into the cytoplasm where HMGB1 binds to cytoplasmic Toll-like receptor 9, leading to p38 activation and subsequent PGC-1α phosphorylation, which eventually enhances mitochondrial biogenesis and thereby promoting tumor growth in HCC [26]. Recent

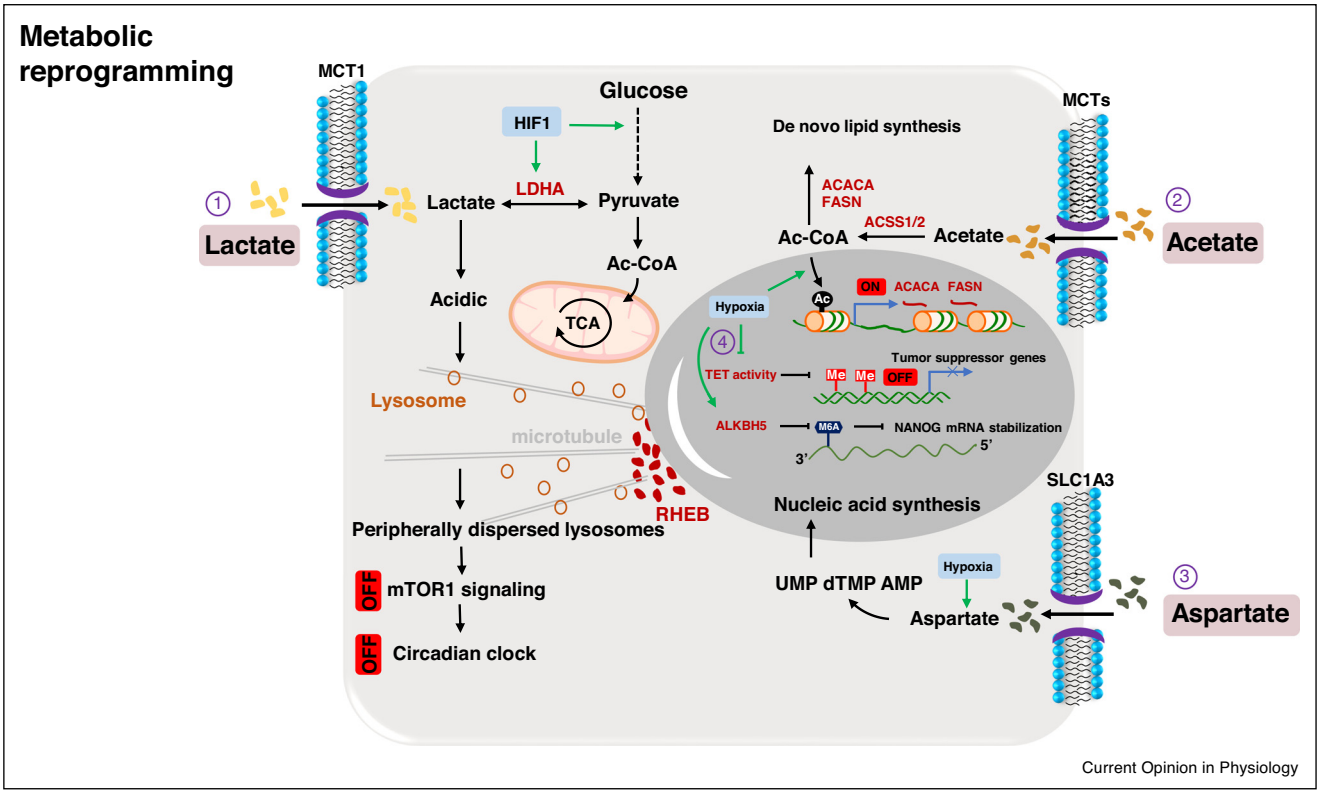
studies also show that hypoxia regulates membrane function via downregulating cell-surface proteome at the global level. More specifically, membrane proteins are internalized by endocytosis through caveolin-1 under hypoxia [27]. Collectively, hypoxia regulates cancer metabolism through multiple ways, including genetic, epigenetic regulation as well as regulation at protein level (Figure 1), and these metabolic reprogramming events help the cancer cells acquire enhanced survival and proliferation ability, through more efficient nutrition uptake from a frequently nutrient-poor microenvironment as well as via selective gene expression or protein translocation.

Tumor immunity under hypoxic microenvironment

Hypoxia signaling in regulating immune responses to assist or resist cancer cell growth has gained continuous attention in recent days. HIFs induce multiple host immune functions, from boosting phagocyte microbicidal capacity to driving T cell differentiation and cytotoxic activity [28]. HIFs are also actively involved in the regulation of immune cell metabolism, including glycolysis and OXPHOS [29]. Since cancer cells are extremely aggressive and frequently face nutrition starvation condition, they need surrounding cells to provide nutrition for their survival. For instance, Sousa *et al.* demonstrated that alanine secreted by stroma-associated pancreatic stellate cells (PSCs) fuels the tricarboxylic acid (TCA) cycle in pancreatic ductal adenocarcinoma (PDAC) [30]. Moreover, ammonia released from liver penetrates into breast cancer microenvironment and provide nitrogen source for breast cancer cell growth [31]. Since Immune cells ubiquitously reside in tumor microenvironment, here, we will focus on the regulation of immune cell function as well as the interactions between cancer cells and immune cells under hypoxic microenvironment mainly from a metabolic point of view.

First, hypoxia can regulate the function of immune cells directly. For example, recent studies have revealed that hypoxia regulates tumor angiogenesis via immune cells. Productive angiogenesis, a prerequisite for tumor growth,

Figure 1



Metabolic reprogramming of cancer cells under hypoxic microenvironment.
Utilization of several unconventional nutrient sources and epigenetic changes have been triggered by hypoxia. (1) Lactate is imported by MCT1 and turned into pyruvate to feed the TCA cycle. In contrast, lactate-induced intracellular acidification suspends the circadian clock by separating lysosomal mTORC1 from its perinuclear activator RHEB under hypoxia; (2) Ac-CoA catalyzed by ACSS1 and ACSS2 from acetate provides acetyl group for histone acetylation and building blocks for *de novo* fatty acid synthesis under hypoxia; (3) Under hypoxic conditions, the limiting metabolite aspartate is a major source for nucleotide biosynthesis; (4) Hypoxia also impedes the transcription of tumor suppressor genes by inhibiting the TET activity as well as stabilizes mRNA via facilitating demethylation of m6A.

brings nutriments and oxygen while non-productive angiogenesis induces high-density network of immature vessels, severe hemorrhage, increased hypoxia and facilitated metastasis. Productive angiogenesis depends on the balanced release of angiogenic and angiostatic factors by different cell types within hypoxic tumors. Krzywinska *et al.* found that loss of HIF-1α in NK cells suppressed the expression of angiostatic soluble VEGFR-1, which led to increased bioavailability of the major angiogenic cytokine vascular endothelial growth factor (VEGF), leading to non-productive angiogenesis and thereby inhibiting tumor growth. In other words, HIF-1α accumulation in NK cells inhibits non-productive VEGF-driven angiogenesis to promote tumor growth [32•]. However, different from NK cells, in tumor-associated macrophages (TAMs), hypoxia promotes the expression of REDD1 to repress the activity of mTOR, thereby, hinders glycolysis in TAMs. Endothelial cells outcompete TAMs for glucose usage that facilitates vascular hyperactivation, leading to abnormal tumor associated angiogenesis to promote tumor metastasis [33]. As is known, immune escape and tolerance are characteristic features of solid tumors. Interestingly, unlike other organs, oxygen is abundant in the lung tissue, which activates PHD proteins to suppress HIFs and glycolysis in lung resided T cells. The inhibited glycolysis promotes induced regulatory T cells (iTreg) differentiation and represses helper T cell-1 (Th1) effector cell differentiation, resulting in immunologically tolerant metastatic niche, which permits cancer cells spread to the lungs [34•].

However, immune responses under hypoxia bring not only benefits but can also kill cancer cells. Palazon *et al.* have demonstrated that HIF-1α drives glycolytic metabolism, infiltration, and effector function of $CD8^+$ T cells to inhibit tumor growth, meanwhile, deletion of VEGF-A, a HIF target gene, in $CD8^+$ T cells accelerates tumorigenesis via decreasing non-productive vascularization [35]. Nutrient deficiency would cause $CD8^+$ tumor-infiltrating lymphocytes (TILs) exhaustion in melanoma. In order to preserve their effector killing functions, $CD8^+$ TILs conduct a metabolic switch to catabolize fatty acids under the tumor microenvironment with limited access to glucose and oxygen O_2 via PPAR-a signaling [36•]. Moreover, hypoxia enhances the proliferation, viability, and cytotoxic function of effector memory T cells (TEM) [37]. These findings highlight that hypoxia promotes cytotoxic function of T lymphocytes for tumor killing.

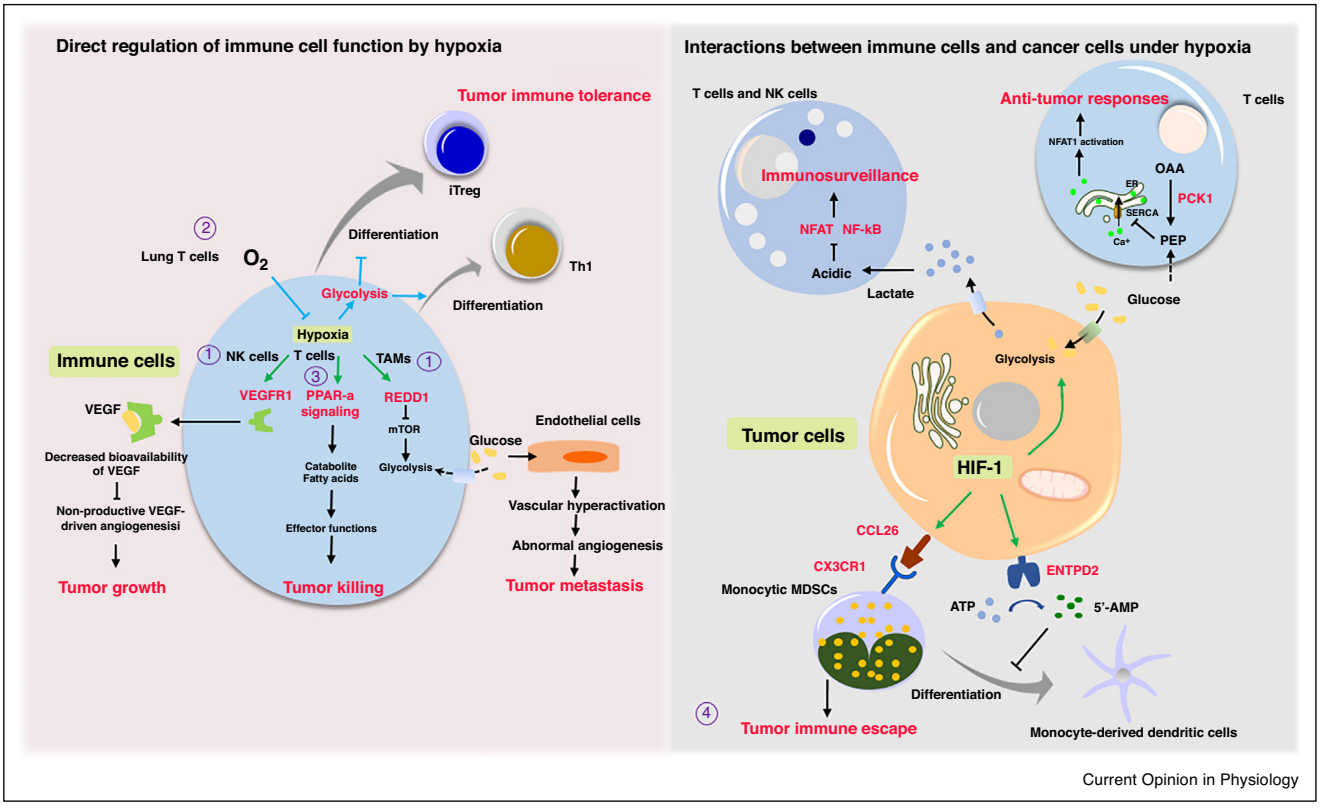
In constrast, hypoxia can also modulate immune cell function by affecting cancer cells. Myeloid-derived suppressor cells (MDSCs) harbor immunosuppressive activities, which permit cancer cells to become non-responsive to immune checkpoints blockade and escape immune surveillance. Chiu *et al.* revealed that under hypoxia, HIFs activates Chemokine (C-C Motif) Ligand 26 (CCL26) expression in cancer cells which binds to its cognate receptor chemokine (C-X3-C motif) receptor 1 (CX3CR1) in MDSCs, recruiting MDSCs to hepatocellular carcinoma (HCC). Utilization of HIFs inhibitors or CX3CR1 neutralizing antibodies blocks MDSCs recruitment to hepatocellular carcinoma and exhibits therapeutic potential [38]. Moreover, ectonucleoside triphosphate diphosphohydrolase 2 (ENTPD2), another direct transcriptional target of HIF-1α, is also remarkably expressed under hypoxia in human HCC. ENTPD2 converts ATP to 5′-AMP, which protects monocytic-MDSCs from differentiating into monocyte-derived dendritic cells. As a result, hypoxia promotes extracellular 5′-AMP production via ENTPD2 and, therefore, maintains MDSCs residing in tumors [39••]. These two articles revealed how cancer cells recruit and maintain MDSCs to promote their immune escape under hypoxia.

More interestingly, cancer cells frequently compete with surrounding immune cells for nutrition. For instance, Chang *et al.* showed that competitive glucose consumption by tumors metabolically restricted surrounding T cells, resulting in suppressed mTOR activity, glycolytic capacity and effector function of T cells, thereby allowing tumor progression [40]. Hypoxia facilitates glucose uptake and glycolysis of cancer cells in the microenvironment. In contrast, immune cells can develop strategies to maintain their tumor killing activity. For example, phosphoenolpyruvate (PEP) sustains Ca^{2+} and nuclear factor of activated T cells (NFAT) signaling by blocking sarco/ER Ca^{2+}-ATPase (SERCA) in T cells to maintain downstream T cell receptor (TCR) signaling and effector functions. However, cancer cells frequently exhaust glucose in intratumoral hypoxic environment, which limit T cells to generate PEP from glucose. In order to maintain their anti-tumor efficacy, intratumoral T cells rewire their metabolic pathways to produce PEP from oxaloacetate (OAA) by activating phosphoenolpyruvate carboxykinase 1 (PCK1) [41]. Finally, acidified tumor microenvironment facilitated by hypoxia decreases cytokine production, in particular IFN-γ, in tumor-infiltrating T cells and NK cells. Mechanistically, lactic acid uptake by CD8+ T cells leads to intracellular acidification, which disturbs the transcription of cytokines by inhibiting the transcription factors such as NFAT and NF-kB, leading to destroyed tumor immunosurveillance and enhanced tumor growth [42••]. Taken together, hypoxia regulates tumor immunity through multiple ways (Figure 2) and continued exploitation would significantly advance immunotherapeutic approaches for cancer therapy.

Concluding remarks and future directions

The rewired metabolism has been recognized as one of the major hallmarks of cancer cells and has attracted tremendous attention continuously in recent years. Meanwhile, the progresses in the field have also provided

Figure 2



Tumor immunity regulated by hypoxia.
Functions of immune cells in the tumor microenvironment are regulated by hypoxia in many ways. (1) In NK cells, HIF-1a enhances the expression of VEGFR-1 to decrease the bioavailability of VEGF, leading to inhibited non-productive angiogenesis and promoted tumor growth. In TAM cells, hypoxia decreases glycolysis and angiogenic response via REDD1-mediated mTOR inhibition, resulting in non-productive angiogenesis and metastasis; (2) In the lung, abundant O_2 activates PHD to destroy glycolysis in T cells, directing T cell differentiation into iTreg rather than Th1 to form the immune tolerant microenvironment; (3) Hypoxia promotes T cells to consume fatty acids to maintain their effector functions and tumor killing. (4) Hypoxia also intervenes immune cell function by affecting cancer cells: HIF-1 increases CCL26 and ENTPD1 expression in cancer cells. CCL26 recruits MDSCs through the cognate receptor CX3CR1 and ENTPD1 converts ATP to 5′-AMP to prevent MDSCs from differentiating into dendritic cells, resulting in immune escape of cancer cells under hypoxia; Glucose competition with cancer cells forces T cells to produce PEP from OAA to sustain Ca^{2+} and NFAT signaling to maintain their effector functions; Lactate induces intracellular acidification of surrounding T cells and NK cells, which inhibits transcription factors such as NFAT, NF-kB and thereby resulting in immunosurveillance.

new opportunities for anti-cancer therapy. It is worth mentioning that IDH1 and IDH2 inhibitors targeting metabolic pathways have been approved by FDA [43]. For targeting hypoxia, HIF-1 inhibitor such as digoxin and *N*-acetyl-L-cysteine (NAC) have been identified [44]. With immunotherapy emitting a growing fascination, research on tumor immunology has received considerable attention. However, spatiotemporal regulation of tumor immunity under hypoxic microenvironment remains largely unexplored. Future studies will be focused to elucidate the intertwined regulation between cell metabolism, tumor immunity and hypoxia, with a hope to provide novel therapeutic opportunities for cancer patients.

Conflict of interest statement

Nothing declared.

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