Targeting Immune Cell Metabolism for the Improvement of Cancer Therapy

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Abstract: It is well-established that cancer cells reprogram the pathways of nutrient acquisition and metabolic preferences to supply the accelerated bioenergetic, biosynthetic, and redox demand due to elevated growth and proliferation rate. The consequent production of metabolites, secretion of chemokines and cytokines, the reduction of pH, and depletion of oxygen availability due to cancer metabolic reprogramming all play a role in affect immune cell activities and contribute to the formation of an immunosuppressive microenvironment. Elucidation of metabolic profiles for both cancer cells and immune cells is a critical topic in understanding the overall metabolic network as well as recognize potential therapeutic targets for cancer therapy. This review provides a general picture of metabolic reprogramming of various immune cells from both innate and adaptive immune systems within TME, the essential pathways and regulators in contributing to the metabolic changes, as well as address the therapeutic potential of the targeting the key determinants for the development and improvement of anti-tumor therapies.

1. Introduction

The aberrantly accelerated growth and proliferation of cancer cells require metabolic reprogramming to bring up an increased nutrients uptake and processing. Cancer cells normally achieve metabolic alternation via manipulation of bioenergetic and biosynthetic pathways as well as modify the tumor microenvironment (TME). It is well-established that cancer cells preferentially switch the glucose metabolism toward aerobic glycolysis to produce lactate, regardless of the presence of oxygen, instead of mitochondrial oxidative phosphorylation (OXPHOS), known as the Warburg effect. Besides glucose, glutamine is another critical carbon source involving in cancer metabolic function via glutaminolysis to generate ATP and lactate, replenishing anaplerosis and macromolecule precursor biosynthesis [1]. The redirected pentose phosphate pathway (PPP) from glycolysis also generates building blocks, such as nucleotide synthesis, to sustain cancer cell growth. As a convergence of signals from both intra and extracellular environment, PI3K/Akt/mTOR signaling pathway is the master regulator of metabolic function and is commonly upregulated in various cancer types to promote the nutrient uptake and biosynthetic pathway [2].

The uncontrolled cell growth in TME with an increased oxygen demand, which often exceeds the oxygen availability from the preexisting blood vessels, creates a hypoxic condition. With the deficiency of oxygen, one important transcriptional factor, HIF is stabilized and induces a metabolic switch to adapt to the environment and better survival; and is also normally hyperactivated in cancer cells to facilitate the metabolic alterations [3]. As a consequence of the accelerated glycolytic pathway and the production of a large amount volume of lactate, TME becomes acidified. The resulted acidification is toxic for normal cells, while cancer cells could survive better in the same environment due to its highly adaptive ability and even with a promoted capacity of metastasis [4]. In addition, due to the limited availability of nutrients and oxygen availability within TME, there is a metabolic competition between cancer cells and normal cells, including immune cells. Not surprisingly, changes in the nutrient availability and environmental conditions reprogram the metabolic pathway, the normal function, differentiation, as well as proliferation of immune cells, which creates an anti-inflammatory condition and immunosuppressive environment [5], [6]. Thus, the pathway involved in the metabolic

alteration of cancer cells in the TME as well as the regulators associated with the immune cell metabolism are novel and promising therapeutic targets to maximize the anti-tumor potential of the immune systems as well as increase the efficacy of existing traditional therapies. Furthermore, even though it has been noticed that the significance of the altered immune cell metabolism in contributing to the formation of immunosuppressive environment and benefiting tumor progression, a clearer picture of the metabolic network of the immune system as well as more detailed mechanistic pathways behind are remained further explored. This review mainly focuses on understanding how cancer cells within the TME induce the metabolic remodeling of T cells, B cells, and macrophages, elucidating some of the most significant signaling pathways and critical regulators contributing to the metabolic changes, as well as the guidance of targeting metabolic pathway to improve immune responses and revert the immunosuppressive status.

2. Targeting t cell metabolism

2.1 Dysfunctional T cell metabolism within TME

T cells undergo metabolic remodeling during activation resulting in the differentiation of distinct subsets with specific immunologic functions [7]. Metabolically quiescent T cells generally produce energy through OXPHOS using glucose, fatty acids, and amino acids as energy fuel. Upon stimulation of antigens as well as the ligation of antigen receptors and co-stimulatory molecules, T cells switch their metabolic preferences from fatty acid oxidation and pyruvate oxidation to glycolysis and glutaminolytic pathway to support the effector function and meet the biosynthetic demands of their growth and proliferation [8].

The activation of T cells triggers the activation of phosphoinositide 3-kinase (PI3K) signaling pathway as well as protein kinase B (Akt) and mammalian target of rapamycin (mTOR) signaling pathway, which results in the expression of HIF1α [9], [10]. A high level of Akt activation was shown to facilitating the trafficking of effector CD8 T cells, highly specialized lymphocytes mediating direct cytotoxic effects on tumor cells, to the inflammation site as well as inducing terminal differentiation [11], [12]. Metabolically, the activation of PI3K/Akt/mTOR activation also enhances the expression of glycolytic enzymes and several glucose transporters to promote glucose and amino acids influx and utilization [13], [14]. HIF-1α -induces the expression of glucose transporters and glycolytic enzymes which all promote the rate of glucose metabolism. Pyruvate dehydrogenase kinase 1(PDK1), one of the enzymes that are activated by HIF-1α, suppressed the conversion of pyruvate to acetyl-CoA by inactivating the function of pyruvate dehydrogenase (PDH). Together with all of the transcriptional regulations, HIF-1α initiates the metabolic switch that redirects glucose processing toward aerobic glycolysis and away from OXPHOS [15]. AMP-activated protein kinase (AMPK) is another critical metabolic regulator of T cells that responds to the changes of AMP/ATP ratio. Specifically, when triggered by low energy status, AMPK would promote the ATP-producing catabolic pathway and suppresses anabolic pathways to maintain cellular energy homeostasis [16]. It also inhibits mTOR activity as well as related anabolic pathways through phosphorylation of TSC2 and raptor protein [17]. Another important function of AMPK is to activate fatty acid oxidation (FAO) by inhibiting acetyl-CoA carboxylase, which at least partially, supports T effector (Teff) to T memory cell transition [16]. In addition, Th1 and Th17 reply on glycolytic activity to support their functions while Treg preferentially use lipid oxidation as the metabolic program to support their growth [18].

Because both cancer and activated T cells rely on aerobic glycolysis, there is a competition for the available nutrients to support their biosynthetic needs[5]. Proliferating tumor cells utilize most of the glutamine, glucose, tryptophan, and other available nutrients creating a nutrient scarcity condition for T cells. The resulted high concentration of metabolites impairs T cell function, metabolism, and survival through the promotion of AMPK signaling and the suppression of PI3K/Akt/mTOR pathway [5], [9]. Moreover, since regulatory T cells (Treg) less rely on glucose metabolism but more on oxidative reaction instead, the altered TME restricts Teff metabolism but promotes Treg activity. Treg suppresses immunity by inhibiting Teff function and thus creates an immunosuppressive

microenvironment [19]. In addition to glucose, amino acid is another important source of mediating the activation of T cells as well as their functions. For example, tryptophan is thought to be a limiting amino acid in regulating T cell activation and effector function. It is locally depleted by indoleamine 2,3-dioxygenase (IDO) and tryptophan-2,3-dioxygenase (TDO) and convert to kynurenine via kynurenine pathway to maintain immune homeostasis by reducing autoimmune responses [20]. The level of kynurenine is positively correlated to Treg activities while inhibits Teff activation [21]. Therefore, they appear to be promising targets for the restoration or activation of anti-tumor immunity. TME also impairs infiltrating lymphocytes through reduction of nutrient availability and excretion of inhibitory signals. For instance, tumor-infiltrating T cells have a persistent loss of the mitochondrial mass and damage of the function within the TME with the gradual reduction of peroxisome proliferator-activated receptor γ (PPARγ) coactivator 1α (PGC1α), which mediates mitochondrial biogenesis and oxidative metabolism and induces tumor-infiltrating T cells metabolic exhaustion [22].

In response to the low level of oxygen within TME, HIF-α is activated to promote the glycolytic pathway, thus an accumulation of lactic acid formed. Studies have indicated lactic acidosis suppresses PI3K/Akt/mTOR pathway and glycolysis thus impair the proliferation and normal function of T cells [5], [23]. Suppression of glycolysis is highly detrimental for effector and cytotoxic T cells as it limits their ability to generate IFN-γ, a pleiotropic molecule that promotes anti-tumor activities, and maintaining intracellular calcium equilibrium [24], [25]. In addition, extracellular lactate and lactic acid could inhibit the migration ability of both CD4 and CD8 T cells through the engagement between CX3C chemokine receptor CXCR3 and CXCL10 [26].

2.2 Targeting the metabolic pathway to enhance T cell function

Since metabolic reprogramming is a critical step for T cell activation and differentiation, and it is commonly dysregulated in TME, different metabolism-regulating factors and metabolic intermediates have gained increasing attention in developing novel immunotherapies. PI3K/Akt/mTOR pathway is a quite promising target since it is commonly hyperactivated in cancer cells to support accelerated bioenergetic activities. A PI3K/Akt/mTOR inhibitor, gedatolisib, have shown encouraging result in treating lymphoblastic leukemia under clinical trials [27]. Interestingly, the development process of memory precursor effector cells is also being affected by the activity of mTOR. Specifically, inhibitors of mTOR facilitate the transition from Teff to memory T cell during T-cell contraction; moreover, the inhibition induced memory T cell even presents a memory recall and protective ability [28], [29].

Another attractive target is AMPK due to its regulation on both metabolic reprogramming and T cell differentiation. Clinical statistics have shown that metformin, a drug that positively regulates AMPK, along with neoadjuvant chemotherapy has increased the pathologic complete response up to 3-fold compared to the patients not taking metformin [30]. One possible explanation for the increased therapy efficacy is that the inhibitory effect of AMPK resulted in dysregulation of downstream signaling pathways and/or impair cell development and proliferation; however, a more complete and detailed mechanism of metformin in cancer cells remained further explored [30], [31]. In addition, the treatment of metformin promotes the differentiation toward memory T cells for both peripheral and tumor-infiltrating T cells with an enhanced anti-apoptotic capacity [32]. However, other research indicates that with metformin-activated AMPK, there is a reduction of T cell proliferation and an increase in Treg cell differentiation and suppression of Th1 and Th17 differentiation [33]. Thus, elucidating the interrelationship between the AMPK pathway and various T cell subtypes and also other immune cells is the prerequisite of its application on anti-tumor therapy as well as avoiding potential side-effects.

Stimulatory and inhibitory signaling pathways also contribute to T cell metabolism reprogramming as well as regulation of its normal function. For example, PD-L1 and other immune checkpoint inhibitors revert the metabolic suppression on T cells through the upregulation of glycolysis-related gene expression and activation of PI3K/Akt/mTORC1 signaling pathway; and the promoted metabolism would facilitate T cells to compete for the limited nutrient sources with cancer cells and generates stronger immune responses and better immune protection [19].

3. Targeting macrhophage metabolism

3.1 Metabolic reprogramming of M1 and M2 macrophages within TME

Macrophages, scavenger cells from the innate immune system, have been thought to play a crucial role in mediating antitumor functions and regulating T cell immune functions [34]. Macrophages could be categorized into either M1 or M2 depends on the extracellular, and intracellular signaling, the resulted immune responses, and metabolic regulations. M1 macrophages preferentially use glycolysis to convert glucose into lactate to generate reactive oxygen species (ROS) and nitric oxide (NO) for the purpose of eliminating tumor cells; M2 macrophages primarily use FAO and citric acid cycle (TCA) cycle to support their growth and proliferation via the positive regulation of PPARγ, STAT6 and PGC1β [35]– [37]. It was known that interferon γ (INF-γ) and lipopolysaccharides (LPS) induce the activation of glycolysis of M1 macrophage through the stabilization of HIF1α as well as its transcriptional up-regulation of glycolysis-related gene expression [3]. Macrophages also synthesize glycogen through glycogenolysis under the stimulatory effect of INF-γ and LPS, then the metabolic intermediate glucose-6-phosphate (G6P) will undergo PPP to generate NADPH and ROS, which is essential in the inflammatory function as well as phagocytic activity of macrophages [35], [38]. The differentiation of macrophages is also regulated by multiple amino acids. For example, the metabolic fate of arginine was shown to be a critical factor in regulating macrophage metabolism and polarization. M1 preferentially metabolizes arginine to NO and citrulline using NO synthase; while M2 macrophages metabolize arginine to ornithine and urea feeding the arginase pathway to produce polyamine and proline, which are essential compounds in cell growth and proliferation and possibly contribute to the support cancer cell survival [39].

M2 macrophages and a small portion of M1 macrophages are classified as tumor-associated macrophages (TAM) due to their contribution in creating an immunosuppressive microenvironment by expressing cytokines, chemokines, and growth factors that would suppress anti-tumor immunity [40], [41]. Endothelial cells in malignancies frequently upregulate the production of angiopoietin 2 (ANGPT2), a proangiogenic cytokine. TEK tyrosine kinase (TIE2)-expressing macrophages are a subset of myeloid cells expressing its receptor and also characterized by angiogenic phenotype [42]. TIE2 expressing macrophages are frequently aligned along the surface of blood vessels due to the endothelial cells ligand-receptor activity [43]; and inhibition of the TIE2 population resulted in suppression in angiogenesis, implying its contribution in vessel formation [44]. Besides the formation of angiogenesis, a subset of TAM, specifically streaming TAMs co-migrate with tumor cells to the intravasation sites and pre-metastatic TAMs are recruited to facilitate the tumor extravasation and metastasis progress [45]. Colony-stimulating factor-1 (CSF1) secreted by tumor cells, is often correlated with poor prognosis [46]; while inhibition of CSF1 causes reduced progression and metastasis of cancers and also a reduced number of TAM [43], [47]. Macrophages within lung cancer upregulate C-C chemokine receptor 2 (CCR2) and CX3CR1 as well as the downstream signaling pathway, includes JAK-STAT and Akt/PI3K. The promotion of the chemokine receptor and their corresponding ligands in both macrophages and cancer cells induce M2 polarization and enhanced cancer cell survival [48]. In addition, TAMs also express cell surface receptors to inactivate immune effector cells through the binding of the death and inhibitory receptors. For instance, TAMs express PD-1 and CTLA-4 ligand receptors, which inhibit the cytotoxic effect of T cells, as well as the normal function of natural killer (NK) cells [49]. Other studies also have shown cytokines produced by tumor cells under hypoxic conditions, such as TGF- β and IL-6 drives the activation of M2 polarization [50].

The lactic acid in the TME, together with the hypoxia, is known to drive macrophage transformation from M1 to pro-tumorigenic M2 phenotype via an HIF1-mediated route by up-regulating M2-like gene expression [5]. The accumulation of lactate and a low level of pH also suppresses pro-inflammatory or M2 activation by suppressing the NF-κB-related signaling pathway [51]. The two isoforms of HIF are also inherently linked to the macrophage polarization: HIF1α, which is induced by the activation of NF-κB, leads to the generation of pro-inflammatory cytokines and promote M1 differentiation; while HIF2α expression occurs without the involvement of NF-κB but does show a correlation with M2 phenotype. The underlying mechanism behind the fate regulation of HIF remains unexplored [52].

3.2 Therapeutic target of macrophage metabolism

It is well-established that macrophages, at least partially, drive tumorigenesis by creating an immunosuppressive environment and also correlated with poor prognosis. One of the strategies of targeting macrophages is to delete or limit macrophage recruitment as thus suppress its overall tumorigenic effect. For example, trabectedin, a recently approved chemotherapy drug that is applied in many cancer treatments, has been shown to exert a specific cytotoxic effect on mononuclear phagocytes, including macrophages while leaving neutrophiles and lymphocytes unaffected. In this way, the number of monocytes/macrophages is being significantly reduced in blood, spleen, and tumors, which resulted in a suppression of angiogenesis and enhancement of anti-tumor activity [54].

Another strategy is to drive repolarization toward M1 and prevent TAM from adopting M2 endotype. Studies have identified several key factors in regulating the signaling pathway associated with polarization at the genomic level. Myeloid-specific Src family kinase member hematopoietic cell kinase (HCK) is identified as one of the critical regulators of the gene expression associated with M2 activation and polarization [55]. Hyperactivated HCK activity is correlated with poor prognosis in human colon cancers. Attempts have been made to suppress the hyperactivation of HCK, which resulted in a reduced M2 differentiation and also a reduction in the colon cancer xenograft [56]. STAT6, as we discussed earlier, is another factor that contributes to the fate decision of macrophages. Knockout of STAT6 in mice has shown resistance to metastatic carcinoma with the induction of M1 macrophages as well as enhanced immunosurveillance [57]. Thus, the result suggests targeting HCK, STAT6, and also other key regulators involved in macrophage polarization fate are promising therapeutic targets to improve the performance of cancer therapy.

4. Targeting B cell metabolism

4.1 B cell metabolism in its activation and differentiation

B cells also experience metabolic reprogramming to differentiate into either plasma cells or memory cells which are able to produce antibodies targeting cancer cells. The binding of B-cell receptor (BCR) with foreign antigens is the first step that simulates the activation of B cells. Alternatively, B cells could also be activated through the binding of antigen to BCR and present the antigenic peptides to T follicular helper cells (TFH) via the co-stimulatory CD40 and other cytokines produced by TFH. Following initial activation of T cells, germinal centers (GC) are transiently formed within the centers of B cell follicles and are characterized by dark zone and light zone. B cells proliferate extensively and undergo somatic mutations to generate different antigen affinities in the dark zone; next, with the positive selection of TFH and antigen-presenting cells (APC), B cells with the highest affinity for the specific antigen will eventually differentiate into plasma cell or memory B cells.

mTOR-related signaling pathway is highly active during pro to pre-B cell development, which is similar to the T cell maturation process. In addition, upon cognation and selection of GC B cells, mTORC1 activity is also activated, which drives the anabolic growth phase and supports dark zone proliferation. Inhibition of mTORC1 has shown to negatively influence B cell accumulation after the positive selection [58]. Another newly identified regulator, protein kinase C β (PKCβ) promotes mTOR-dependent mitochondrial remodeling, germinal center formation and drives plasma cell differentiation [59]. PI3K/Akt signaling pathway has also been activated when BCR recognizes antigens; the activated Akt phosphorylates the transcriptional factor FOXO, which directs the program of blocking cell cycle progression and promote the expression of pro-apoptotic genes, and leads to the subsequent degradation in the cytoplasm [60]. PI3K is also involved in the immature B cell fate regulation: co-incubation with PI3K inhibitors resulted in a suppression of Rag2 expression, an essential enzyme for the maturation of pre-B cells, suggesting BCR as well as B cell development are relied on PI3K activation [61]. Akt is activated to induce the activity of HIF-1α [62], which elevates glucose influx via upregulation of glucose transporters expression. However, based on data from metabolite tracing, there is a high level of glucose import, but the glycolytic metabolites did not increase over time, indicating there might be an alternatively metabolic pathway in contributing the

activation of B cells [63]. HIF-1α also regulates B cell differentiation and proliferation: mouse embryos with HIF-1α-deficient have been shown to have abnormal peritoneal B-1 like lymphocytes, impair in B-2 lymphocyte distortion, and also autoimmunity problem [64]. Moreover, activated B cells also upregulate OXPHOS and TCA cycle, but relatively low glucose was used to feed the cycle, indicating an alternative carbon source, such as glutamine, is being used to support the metabolic activities [63]. Research also has shown that long-lived plasma cells have accelerated glutamine intake and used it for both mitochondrial respiration and anaplerotic reactions, the generated metabolites are essential for antibody synthesis [65].

4.2 Dysfunctional metabolism in B-cell malignancies and potential therapeutic targets

There is an intimate correlation between B cell malignancies and dysregulated B cell metabolism. B-cell-derived non-Hodgkin lymphoma (B-NHL) is often characterized by a hyperactivated mTOR signaling pathway which facilitates increased glycolysis and OXPHOS of cancer cells to support their proliferation and survival. This can be achieved by the hyperactivity between BCR and PI3K/Akt signaling pathway or through PI3K/Akt independent manner, such as the loss of function of PTEN, a PI3K/Akt inhibitor [66]. The effect of mTOR Inhibitors was evaluated in refractory/relapsed diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), and mantle cell lymphoma (MCL) [67]; but the clinical results is less encouraging than the preclinical studies potentially due to the heterogeneity of cancer cells as well as incomplete disruption of the signaling cascade. A combination of PI3K and mTOR inhibitors displayed a higher efficacy in treating BNHL in vitro and in vivo studies [68]. Other clinical trials combines mTOR inhibitors with anti-CD20 based chemotherapies, such as R-CHOP. CD20 is exclusively expressed on the surface of B cells and is widely expressed in FL, DLBCL, and MCL, which cooperate wither other factors to induce hyperactivation of mTOR. The overall response rate (ORR) and complete response (CR) in refractory/relapsed MCL is shown to be higher than the ORR and CR treated with either mTOR or anti-CD20 alone [67].

There are also pre-clinical attempts in reverting the therapeutic resistance via targeting the metabolic pathways. Ibrutinib is an oral inhibitor of Bruton's tyrosine kinase (BTK), which is widely activated in B cell lymphomas. Transcriptomic profiling data indicate that metabolic reprogramming, specifically toward OXPHOS and glutaminolysis, is strongly correlated to ibrutinib resistance in MCL. A clinical inhibitor, IACS-010759, targeting the complex I of mitochondrial electron transport chain have has been applied in treating ibrutinib-resistant patient-derived cancer models. The results show that IACS-010759 reduced the ibrutinib-resistant MCL cell line as well as primary MCL clinical specimen isolated from patients via suppression of proliferation and promotion of apoptosis [69].

BTK inhibitors and PI3K inhibitors combined with standard chemotherapy have also been used to treat chronic lymphocytic leukemia (CLL). Both strategies have shown encouraging efficacy in clinical trials, and the combination of PI3K inhibitor idelalisib with standard chemotherapy even showed improved overall survival compared to chemotherapy alone [70]. Despite the presence of oxygen in the bloodstream, CLL still constitutively expresses HIF-1α and produces lactate via glycolysis. Inhibition of HIF-1α using chetomin reduced glucose consumption but glutamine consumption was elevated. Therefore, the TCA cycle is facilitated by glutaminolysis as well as the production of metabolites, like glutamate, pyruvate, and lactate [71]. Studies also indicate CLL cells carry a relatively more mitochondrial mass than normal B lymphocytes. NO promotes mitochondrial biogenesis, which is regulated by PPARγ. NO supplementation elevated mitochondrial mass in B-NHL cell lines while inhibition of NO results in the opposite, suggesting its role in facilitating tumor cell growth via accelerated mitochondrial biogenesis [66], [72].

5. Discussion

Due to the accumulation of metabolites derived from cancer cell metabolism as well as the changes in the environmental condition, immune cell metabolism is being greatly affected and also the consequent differentiation or polarization process. Manipulating the metabolic pathway of immune cells to either sustain the activation status of anti-tumor immunity or deplete immunosuppressive

immunity is one of the main strategies of therapy development. Moreover, targeting the metabolic pathway or inhibitory signaling, such as PI3K/Akt, mTOR, and PD-1 blockade displayed positive results in both pre-clinical and clinical trials via accelerating immune cell metabolism or activating T cell transcription factor to restore or enhance their effector function.

It is worth highlighting that M1 macrophages, Teff, and cancer cells share some similarities in terms of metabolic programming. Since all of them are considered highly proliferating cells thus they are characterized by accelerated biosynthetic metabolism and anabolism with high rates of glycolysis and glutaminolysis to support their growth and expansion. In contrast, Treg, M2 macrophages, memory T cells, and quiescent cancer cells are primarily characterized by catabolic metabolism and FAO to generate ATP [73]. Novel targets of manipulating the metabolic pathway on immune cells should evaluate the consequent responses of cancer cells. In addition, the development of therapy targeting the essential metabolic pathway should take into account of the similarities in bioenergetic and biosynthetic processes between cancer cells and proliferating immune cells. Therefore, targeting the pathways that are not directly overlapped between cancer cell or immune cells or targeting with better selectivity is more promising in term of future drug or therapy development. In addition, the combination between the metabolic inhibitor with traditional therapy, like chemotherapy and immune checkpoint inhibitors, also demonstrated improved therapeutic efficacy in pre-clinical and clinical trials, thus it could be another direction of developing or improving anti-tumor therapies.

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