Cancer Metabolism and Aggressive Tumor Behavior

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Abstract

Aggressive tumor behavior poses a serious threat to the success of cancer therapy. Altered cancer metabolism is a hallmark feature of tumor initiation, progression, and metastases. During these processes, the tumor cells suffer bioenergetic and nutrient demand, which is met by metabolic reprogramming or preferential nutrient usage facilitated by the acquisition of driver oncogenic mutations and inactivation of tumor-suppressor genes. The metabolic heterogeneity and plasticity of tumor cells provide cellular fitness and survival advantage in the harsh tumor microenvironment (TME), resulting in aggressive tumor growth and resistance to chemotherapies. Besides, other cell types, including stroma, immune cells, and extracellular matrix in the TME, undergo metabolic switching that

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influences disease progression. Because aberrant glucose metabolism is central to tumor cell metabolic reprogram, various clinical trials targeting glucose uptake and its metabolites in combination with other molecular targets have been focused on reducing tumor progression by inhibiting the metabolic interplay. Here, we describe in detail how the metabolic plasticity of cancer cells and TME results in tumor progression and aggressiveness. In addition, we highlight the current approaches being explored for therapeutic intervention. This overview will help in understanding the intricated metabolic networks and open new avenues of cancer treatment.

Keywords

Glucose metabolism · Heterogeneity · Cancer stem cells · Immune cells · Hypoxia · Tumor progression · Lactic acid · Chromatin

2.1 Introduction

Metabolic alterations are a characteristic hallmark feature of tumor cells, facilitating tumor cell proliferation, invasion, immune evasion, and metastases [1]. These aggressive features impose a serious therapeutic hurdle in cancer treatment [1] and are responsible for almost 90% of cancer-related mortality and morbidity [2]. Typically, cancer metastasis involves three main steps—invasion, intravasation, and extravasation. The initial step of metastasis involves detachment of tumor cells from the primary site and invasion of the local milieu directly via blood vessels (intravasation) or lymphatic system. The invasion or dissemination of tumor cells from the primary site to surrounding tissue/stroma occurs either as single cells or clusters [3, 4]. However, only a small subset of disseminated tumor cells survive the shear stress and protective immune cells attached to the endothelial linings of blood vessels and extravasate to facilitate successful metastasis [5].

The tumor mass also harbors a small population of "stemlike" cells known as cancer stem cells (CSCs) that influence various aspects of tumor biology. CSC was first identified in acute myeloid leukemia in 1994 and its potential role in tumor aggressiveness, therapy, relapse, and metastasis of hematological and solid tumor cells was subsequently recognized [6, 7]. These CSCs (0.05–1%) are characterized by the expression of distinct surface markers based on the origin of tumors [8]. Like pluripotent stem cells, CSCs show several salient features such as surviving for longer periods, quiescence, resistance to apoptosis, and ability to undergo self-renewal and differentiation [6, 7]. Such self-renewal property allows CSCs to initiate uncontrolled proliferation with diverse molecular, cellular, and metabolically active phenotypes, subsequently resulting in the significant increase in heterogeneity of primary and metastatic tumors [7, 9]. The acquisition of heterogeneous tumor phenotypes increases the survival advantage during treatment with chemotherapy causing therapy resistance and relapse in various cancer types [9, 10]. To fulfill their energy and biosynthetic demand, tumor cells and CSC increase their nutrient uptake

(glucose and glutamine) from the environment [1, 11]. The marked increase in the glucose consumption by tumor cells compared to normal cells in the presence of oxygen (O_2) was first discovered by Otto Warburg (1926) and is known as the Warburg effect [12]. The Warburg effect is well established in a variety of tumors [1] and has been exploited for tumor diagnosis and staging by positron-emission tomography (PET) using radiolabeled glucose analog ^{18}F-fluorodeoxyglucose (^{18}F-FDG) [13].

Altered cancer cell metabolism is associated with various stages of tumorigenesis. As altered metabolism enhances the cellular fitness of tumor cells by increasing the nutrient uptake, it is essential to understand how these nutrients are utilized, and what metabolic changes occur as a result of preferential nutrient uptake in the tumor microenvironment (TME) in order to promote the tumor progression [1].

This chapter describes in detail the role of altered glucose metabolism in tumor progression and metastasis, metabolic heterogeneity of CSCs, and its association with chemoresistance. In addition, we summarize how the metabolic plasticity of tumor cells influences the TME, leading to disease aggressiveness or therapeutic resistance. We also highlight the potential therapeutic approaches being used to target cancer metabolism.

2.2 Altered Glucose Metabolism in Tumor Cells

Human somatic cells cultured in petri dish undergo limited cell division and become senescent to die due to the "Hayflick limit" named after the first observation by Leonard Hayflick in 1961 [14]. However, tumor cells overcome this "limit" to facilitate limitless cell division, by accumulating oncogenic mutation, inactivating tumor-suppressor genes, and sustaining telomerase activity. This process is driven by the metabolic rewiring of tumor cells to improve their cellular fitness and selective survival advantage [1]. Typically, in normal cells, the influx of glucose is driven by extracellular signals rather than bioenergetic demand. For instance, mammary epithelial cells cultured in detached condition from extracellular matrix have suppressed glucose uptake despite high glucose present in the medium, resulting in decreased mitochondrial function and ATP production [1]. However, constitutive activation of AKT alone can stimulate glycolysis to restore the mitochondrial function and maintain ATP levels despite growth factor deprivation. In normal cells, glucose diffuses into the mitochondria, where it enters the tricarboxylic acid cycle (TCA) to oxidize glucose to carbon dioxide and generate NADH and $FADH_2$ molecules with a little amount of lactate generation via oxidative phosphorylation (OXPHOS) pathway. NADH and $FADH_2$ then enter the electron transport chain to generate net two ATP molecules per glucose consumed.

In 1926, Otto Warburg observed that cancer cells preferentially utilize glycolysis even in the presence of O_2 to support their energy requirement (Warburg effect) [12]. The aerobic glycolysis generates building blocks for macromolecules (proteins, lipids, and nucleotides) required to maintain enhanced growth and proliferation of cancer cells [1]. However, aerobic glycolysis is highly inefficient as it generates only

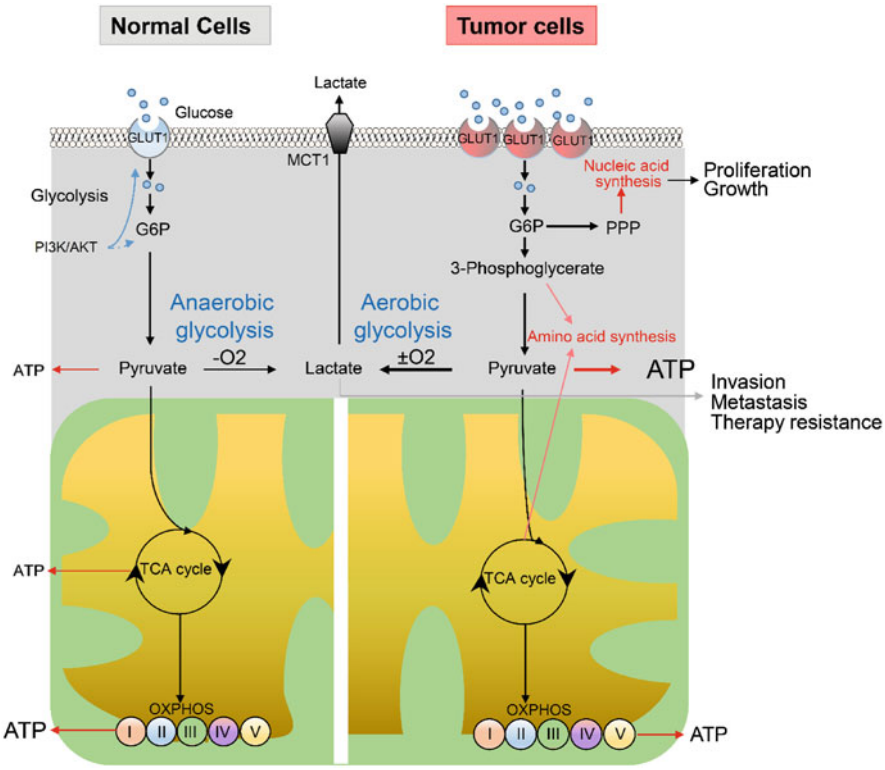

Fig. 2.1 Metabolic reprogramming in tumor and normal cells

two ATP molecules per molecule of glucose metabolized compared to 36 ATP molecules generated via OXPHOS. This low energy production is compensated by PI3K/AKT signaling, a key master regulator of glucose uptake. During PI3K/AKT signaling, AKT drives the transcription of the glucose transporter GLUT1 and its translocation to the cell surface.

AKT also induces the hexokinase (HK) activity to phosphorylate glucose and prevents effluxing of glucose back to the extracellular space. In addition, AKT also activates the phosphofructokinase and thus promotes the irreversible function of glycolysis. Increased GLUT1 and HK activity increases the glucose uptake by 100-fold in tumor cells, leading to the generation of more ATP molecules during aerobic glycolysis than OXPHOS [12]. However, during aerobic glycolysis, the tumor cells generate high amounts of lactate as a by-product (Fig. 2.1). Inhibiting this pathway by inhibitors targeting PI3K or receptor tyrosine kinases can result in the blockade of glucose uptake by the tumor cells [15, 16]. Moreover, aberrant activation of the PI3K/AKT pathway is shown to induce growth factor-independent tumor progression [1].

Apart from PI3K/AKT signaling, oncogenic proteins such as Ras are known to increase the transcription of *GLUT1* [17, 18]. In pancreatic cancer, *Kras* mutation is

an early oncogenic insult that initiates pancreatic intraepithelial neoplasia development and later progresses to pancreatic ductal adenocarcinoma (PDAC) with additional genetic mutations, including Trp53. Increased glycolysis is a key feature of *Kras*-driven tumorigenesis [17, 19]. Abrogation of *Kras* signaling in the PDAC murine model has been shown to result in tumor regression along with severe reduction of *Glut1* transcription and rate-limiting glycolytic enzymes [20]. Apart from elevated glycolysis, *Kras* also fuels the glycolytic intermediates to pentose phosphate and hexosamine biosynthesis [20]. At the molecular level, *Kras*-driven glycolysis is mediated by the activation of MAP kinase, which increases the *cMyc*-dependent transcription of glycolytic enzymes. During cellular stress, such as starvation, mutant *Kras* cooperates with other antioxidant enzymes such as paraoxonase 2 (*Pon2*) to increase glycolysis in PDAC [21]. In lung cancer, mutant *Kras* is responsible for metabolic heterogeneity and metabolizes the glucose differently based on the degree of lesion (low to high grade) in $Kras^{G12D}$;$Trp53^{-/-}$ lung tumors [22]. In addition, lung cancer patients and NSCLC cell lines (49%) also gain homozygous mutation for *Kras* (G12D) [23, 24], which influences the glycolytic switch, maintenance of redox balance, channeling of glucose metabolites to the TCA cycle, and biosynthesis of glutathione [22, 25]. Increased glutathione in the homozygous mutant *Kras* in NSCLC protects the cells from reactive oxygen species (ROS)-mediated abnormalities, thereby increasing the selective growth of these cells during lung tumor progression [26].

2.3 Cancer Stem Cells Exhibit Heterogeneous Metabolic Characteristics

Stem cells are undifferentiated cells with a unique capacity for self-renewal and multiple differentiation in multicellular organisms [27, 28]. As somatic cells have limited cell division, replenishing of the damaged cells is achieved by stem cells and self-renewing its progenitors for maintaining the tissue homeostasis. At physiological condition, stem cells reside in the hypoxic microenvironment, which enables them to maintain their undifferentiated state, proliferate, and commit to cell fate [29]. Due to spatial residence, stem cells rely heavily on anaerobic glycolysis to support their energy requirement [30]. The reliance of stem cells on glycolysis is due to fewer or immature mitochondria, which protects the genome from ROS generated by OXPHOS and limits oxidation of proteins and lipids [31]. A key driver for glucose metabolism in a low-O2 environment is the activation of transcription factor hypoxia-inducible factor 1 α (HIF1α). During anaerobic glycolysis, HIF1α heterodimerizes with HIF1β to promote the transcription of glycolytic genes [32]. The hypoxic condition stabilizes the HIF1α protein by preventing hydroxylation and facilitates the expression of pyruvate dehydrogenase kinase (PDK2 and 4) to prevent pyruvate from entering into the TCA cycle, thus blocking mitochondrial respiration. However, depletion of HIF1α in stem cells results in the reversal of this phenotype, thereby allowing the cells to undergo mitochondrial respiration rather than glycolysis. The transition from glycolysis to mitochondrial respiration is

responsible for the exhaustion of hematopoietic stem cells, and thus suggests the pivotal role of HIF1α in maintaining the hematopoietic stem cell function [33].

Like stem cells, CSCs have the ability to self-renew and maintain an undifferentiated state, remain quiescent, and activate DNA repair machinery. CSCs are associated with tumor initiation, relapse, therapy resistance, and metastatic dissemination [7, 10]. Several studies have identified and characterized CSCs in various malignancies for use as biomarkers or targeted therapies [34]. The stemness features are tightly regulated by several transcription factors (TF) such as OCT4, SOX2, KLF4, and Nanog. Shinya Yamanaka, in 2006, first demonstrated that four TFs (Oct4, cMyc, Sox2, and Klf4) could induce pluripotency in the mouse embryonic fibroblast suggesting the importance of TFs in stemness [35]. Like cancer cells, CSCs also undergo metabolic adaptation to the cellular environment, such as hypoxia versus normoxia and proliferative versus quiescence. Such changes in the cellular environment cause a shift in the metabolic states that gives rise to cellular heterogeneity in CSCs [11, 36]. The existence of heterogeneity in tumor cells and CSCs represents a major therapeutic hurdle in several cancers.

Though CSCs are metabolically very active, controversy regarding their energy metabolism (glycolytic or mitochondrial respiration) is still under scrutiny. In general, glycolytic activity is mainly responsible for maintaining the stemness traits of stem cells, embryonic stem cells, and induced pluripotent stem cells. For example, increased glycolysis in non-small cell lung cancer (NSCLC) leads to the elevation of ABCG2 transporter in the side population [37] via activation of the AKT pathway. Constitutive expression of active AKT also increases the glycolytic rate and aerobic glycolysis independently of the growth factor [37, 38]. Apart from glycolysis, CSCs also utilize OXPHOS for alternative energy generation in response to their physiological needs, suggesting its metabolic flexibility. Recent findings have shown that liver CSCs are highly OXHPOS dependent compared to the non-stem cells, which was evident from increased mitochondrial DNA copy number, mitochondrial content, and ROS. In addition, as a result of the treatment with 2-deoxy-D-glucose (2-DG), the high OXPHOS liver CSCs promote the expression of stemness surface markers CD133 and CD44 [39]. Overall, we now understand that CSCs can undergo metabolic reprogramming (glycolysis or OXPHOS) to support their stemness.

2.4 Metabolic Plasticity Drives Cancer Cell Metastasis

As tumor cells are highly active metabolically, there is a dramatic change in the TME with increased hypoxia, nutrient shortage, and lactic acid buildup. Most of the metabolic pathways are interconnected and flexible, allowing the tumor cells to reprogram their metabolic activity for glucose catabolism and maintain the redox balance during changing microenvironment. The metabolic plasticity ensures the survival of the tumor cells by increasing their cellular fitness during nutrient starvation. For example, in the case of chronic glucose starvation in serous ovarian cancer cells, tumor cells undergo metabolic reprogramming to generate cell types that are highly heterogenic. Such generation of heterogenic cell types is driven by the

ZEB1-dependent transcription of NNMT (nicotinamide N-methyltransferase), which is highly expressed in the metastatic and recurrent tumors compared to matched primary carcinoma. In addition, ZEB1-dependent expression of NNMT also confers resistance to glucose dependence and increases the migration of ovarian cancer cells suggesting metabolic adaptation during glucose restriction [40].

Tumor cells increase their metastatic potential by metabolic reprogramming by shifting from glycolysis to OXPHOS [41]. The metabolic shift to OXHPOS is coordinated by transcriptional coactivator PGC-1α (peroxisome proliferator-activated receptor-gamma coactivator-1α), a key regulator involved in mitochondrial biogenesis and metabolism [42]. Recent studies using the systems biology approach by utilizing AMPK and HIF1 signatures in The Cancer Genome Atlas indicated the presence of a hybrid phenotype that enables the cells to consume various types of nutrients [41, 43]. It also provides cellular advantages such as efficient energy production through multiple metabolism pathways, synthesizes biomass for rapid cell proliferation, and maintains ROS at a moderate level to favor ROS-mediated signaling [44]. Such phenotype was evident in circulating tumor cells isolated from highly metastatic mouse basal type breast cancer cell line (4T1) [45]. The hybrid phenotype is characterized by high levels of HIF1/pAMPK (AMP-activated kinase), which favors both glycolysis and OXPHOS. In contrast, another phenotype with high HIF1/low pAMPK expression and low HIF1/high pAMPK expression in triple-negative breast cancer exclusively favored glycolysis and OXPHOS, respectively [41]. Such metabolic plasticity creates a major clinical hurdle, considering that the current clinical strategies targeting metabolism have been largely ineffective. Thus, simultaneous targeting of both the pathways (glycolysis and OXPHOS) may be critical to eliminate these metabolically highly flexible tumor cells [41, 46].

2.5 Lactic Acid Secretion, Utilization, and Tumor Progression

As a result of increased metabolic rate in tumor cells, there is a significant accumulation of lactic acid and H^+ in the cytosol. Almost 85% of the incoming glucose is converted to lactic acid, which needs to be eliminated from the tumor cells to prevent acidosis and support higher rates of glycolysis. This elimination of lactic acid and H + from the cytosol to the microenvironment is assisted by the increased expression of monocarboxylate transporter isoforms (MCT1 and 4) and Na-driven proton release, respectively [47, 48]. Overexpression of MCT1 and 4 has been associated with poor prognosis and high mortality in several cancers [47]. The dependence on MCTs to expel lactate is based on the fact that lactic acid is a weak acid, which prevents them from diffusion across the membrane. However, studies have shown that the dissociation of lactate to H+ generation is not the primary cause for acidosis. Rather the coupling of ATP hydrolysis and glycolysis is the major source of H+ production which contributes to acidification (low pH) [49].

Heterogeneous distribution of glucose in the intratumoral area, apart from activating HIF1α, also activates the oncogene cMYC to upregulate LDHA (lactate dehydrogenase A), leading to the generation of NAD+ which in turn activates

glycolysis, thus maintaining the vicious cycle [50, 51]. Besides HIF1α and cMYC, lactate also regulates the transcription of *RAS*, *PI3KCA*, *E2F1*, tumor-suppressor genes (*BRCA1* and *BRCA2*), and genes that mediate cell cycle and cell proliferation [52]. On the contrary, cMYC and tumor suppressor P53 also activate the transcription of *MCT1* to favor lactate uptake [53, 54]. HIF1α activates the transcription of *MCT4* to expel lactate from the cells [55]. Under physiological conditions, lactate concentration in the blood and normal tissues ranges between 1.5 and 3 mmol/L [56]. The levels can rise up to 40 mmol/L concentrations in tumors [57]. When lactate is not eliminated from the cells, it can lead to lactic acid acidosis, which is common in most highly mitotic tumors. Tumor-associated acidosis was first documented in acute leukemia patients in 1963 [58]. In general, lactic acid acidosis in cancer patients results from a failure in lactate clearance from the liver due to deficiencies in thiamine and/or riboflavin. Thiamine functions as a cofactor that facilitates the conversion of pyruvate to acetyl-CoA by pyruvate dehydrogenase. Due to thiamine deficiency, this conversion from pyruvate to acetyl-CoA prevents the entry of the latter into the TCA cycle [59]. Thus, balancing lactic acid production and expulsion by cancer cells is essential to prevent intracellular acidification and apoptosis.

Though lactate was previously considered as a "metabolic waste" product of glycolysis, recent studies have demonstrated the role of lactate levels in driving tumor progression, immune escape, angiogenesis, cell migration, and drug resistance [51, 56]. TME is composed of stromal cells, endothelial cells, and immune cells. Immune cells primarily surveil the body to eliminate any pathogen, including tumor cells. However, tumor cells release anti-inflammatory cytokines and recruit immunosuppressive cell types in the TME to inhibit the immune response [60]. Lactate accumulation also dampens the antitumor activity of NK cells and NKT cells by inducing apoptosis [61, 62]. In several tumors, tumor-associated macrophages undergo polarization in response to lactate-induced transcription of vascular endothelial growth factor (VEGF) and arginase 1 [63]. Furthermore, lactate also assists the tumor cells in evading immune response by expressing its receptor G protein-coupled receptor 81 (GPCR81). In lung cancer cells, the activation of GPCR81 receptor results in the upregulation of programmed death-ligand 1 (PD-L1) in the membrane, which blocks the antitumor immune response. On the contrary, blocking the LDHA enzyme which converts pyruvate to lactate in the tumor cells increases the efficiency of programmed cell death 1 (PD1) therapy [64].

Higher lactate in the TME is associated with an increased metastasis in various cancers [48] and correlates with poor clinical outcome [56]. The mechanisms by which lactate promotes metastasis are multifactorial: (1) modifies several cell adhesion molecules, such as integrins, which assist in cell binding to the extracellular matrix, making them more migratory [65], and (2) induces the expression of proteases (MMP9, cathepsin B, and hyaluronidase) to degrade the surrounding tissues, thereby allowing tumor cells to metastasize [66, 67]. Apart from metastasis promotion, lactate buildup is also associated with the induction of therapy resistance. In NSCLC, prolonged treatment with tyrosine kinase inhibitors (EGFR and MET) results in a metabolic shift towards increased glycolysis and lactate production. This

lactate, in turn, promotes the secretion of hepatocyte growth factor by cancer-associated fibroblast (CAF) in an NFkB-dependent manner to activate MET signaling to induce therapy resistance [68]. Thus, targeting lactate metabolism or uptake has proven to be an important strategy for cancer therapy.

2.6 Glucose Metabolism, Chromatin Structure, and Chemoresistance

Changes in the global chromatin structure are associated with gene expression, DNA repair, and tumor progression [69]. Typically opening and closing of chromatin structure is facilitated by the acetylation of histones (H3, H4, H2A, and H2B in nucleosome core) catalyzed by the balanced action of histone acetyl transferase (HAT) and histone deacetylase (HDACs). During harsh metabolic reactions, tumor cells meet the increasing demand for energy and precursors for biosynthesis by initiating the distinct transcription of metabolic genes via chromatin remodeling [70]. The metabolites generated during the metabolic reaction are taken up by the cells actively or passively through the plasma membrane or nuclear membrane to modify the chromatin structure or processed by the metabolic enzymes to function as a substrate or cofactor for the chromatin-remodeling enzymes. Acetyl-CoA is one such metabolic by-product that functions as a substrate for HAT activity. The canonical histone acetylation involves addition of acetyl group at lysine residue which is derived from the metabolite acetyl-CoA. Acetyl-CoA generated during glucose metabolism is funneled through mitochondrial metabolism via a citrate intermediate, which is exported and lysed in the cytosol by ATP-citrate lyase to generate acetyl-CoA. Therefore, nutrient availability is vital in regulating the chromatin structure and gene expression during metabolic reprogramming.

The study by Liu et al. (2015) has shown that inhibiting glycolysis with 2-DG or silencing two rate-limiting enzymes, hexokinase-1 (HK1) and pyruvate kinase (PKM), results in condensing of the chromatin structure and reduced tumor cell proliferation [71]. Besides, increased glycolysis results in higher accumulation of cellular acetyl-CoA, a substrate for acetyltransferases, which increases the histone acetylation, thereby enabling the cells to undergo efficient DNA repair and induce chemoresistance [71].

Another chromatin-associated protein, MORC2, a member of the Microrchidia family CW-type zinc finger (MORC) family of proteins, is upregulated in several cancers [72]. It also regulates transcription by modifying the chromatin structure [73, 74]. During tumorigenesis, MORC2-mediated transcription is catalyzed by the interaction with histone HDAC1, HDAC4, and EZH2 [75]. Likewise, during glucose metabolism, cMYC directly targets the expression of *HK2*, *PFKM*, *ENO1*, *GLUT1*, and *LDHA* [76], while MORC2 is known to regulate *LDHA* by cooperating with cMYC to promote the migration of breast cancer cells [75, 77, 78]. As numerous metabolic pathways converge onto cMYC regulation, attempts to block or restore altered pathways driven by cMYC can lead to novel strategies in cancer treatment.

2.7 Cross Talk Between Tumor Microenvironment and Metabolism in Disease Progression

As discussed earlier, metabolic plasticity allows tumor cells to adapt themselves to changing TME [1]. Aberrant tumor vasculature in the TME causes heterogeneous perfusion (O_2 and nutrients) across the tumor vessels, which promotes a hypoxic environment [79]. The competitive metabolic milieu in the TME also results in the variable nutrient utilization among tumor cells, immune cells, and stromal population [80, 81]. Besides, tumor cells adapt to their metabolic needs in the hypoxic conditions of TME through HIF1, which activates enzymes of glycolytic flux. Overall, the intratumoral metabolic heterogeneity by the nonuniform distribution of nutrients is influenced by various factors, including the composition of TME, disease stage, and mutation load [82]. Here, we will discuss in detail how stroma, extracellular matrix (ECM), and immune cell metabolism are reprogrammed by tumor cells and influence the disease progression.

***Stroma*:** The contribution of stroma for tumor growth and progression is well established in different cancers, but how alterations in stromal composition support tumor growth are still unclear. The metabolic interplay between cancer cells and TME is a well-recognized hallmark of tumors. The accumulation of different metabolic intermediates and their by-products in the TME activates stromal cells through paracrine signaling and alters their phenotype [83]. Stroma modulation by growing tumor is synonymous to the regeneration of damaged tissue and involves (a) monocyte recruitment and activation to pro-inflammatory M1 phenotype for clearance of necrotic tissue and subsequent transition to M2 phenotype; (b) fibroblast recruitment, their differentiation to myofibroblasts, and secretion of ECM for surrounding cells survival; and (c) immunosuppressive milieu characterized by T_{regs}, M2 macrophages, and myeloid-derived suppressor cells [84]. This stromal regeneration by tumors is driven by alteration of metabolic consumption in the TME, which includes autophagy in stromal fibroblasts by glucose depletion and AMPK activation and secretion of nonessential amino acids, which leads to enhanced tumor growth [85, 86]. CAFs are the main component of tumor stroma and engage in tumor progression by promoting tumor cells to undergo EMT and enhancing the stem cell traits and metastatic dissemination [87, 88]. Accumulating evidence shows that CAFs undergo metabolic reprogramming during their activation, including utilization of aerobic glycolysis and increased autophagy for mobilization of the nutrients into the TCA cycle [89, 90]. Also, CAF-derived exosome is seen to mediate metabolic reprogramming [91]. While in PDAC, the oncogenic mutation is observed to regulate signaling in both the tumor cells and adjacent stromal cells. By cell-specific proteome labeling and multivariate phosphoproteomics, it is observed that tumor cell KRAS (KRASG12D) interacts with fibroblast to initiate reciprocal signaling in tumor cells. This reciprocal signaling results in distinct tumor cell phosphoproteome, which regulates tumor cell proliferation and apoptosis and increases mitochondrial capacity [92]. Tumor cells also interact with the CAFs and reprogram their cellular metabolism to adapt to the nutrient deprivation in the harsh TME. One such classic

example is the reciprocal interplay between prostate cancer cells and CAFs which results in EMT and metabolic shift in the tumor cells. As prostate cancer cells come in contact with CAFs, it reprograms the metabolism of cancer cells towards aerobic metabolism, thereby decreasing the dependence on glucose and shift towards aerobic metabolism. This process is driven by reducing GLUT1 expression and increasing the lactate load by MCT1. Therefore, prostate cancer cells by inducing symbiosis with CAFs utilize their by-products, favoring them to grow in a low-glucose environment [88]. While MCT1 can induce lactate uptake or secretion in cancer cells, MCT4 promotes lactate efflux in CAFs through HIF1α induction under hypoxic conditions and results in tumor promotion [93]. In fact, triple-negative breast cancer patients with high stromal MCT4 expression show poor prognosis [94]. In addition, stroma-associated pancreatic stellate cells also secrete nonessential amino acids, decreasing the tumor cell dependence on glucose and serum-derived nutrients [85]. Likewise, CAFs in ovarian tumors utilize carbon to produce glutamine for cancer cells. This shows the existence of novel cross talk between tumor cells and CAFs in metabolic regulation of tumor cells [95]. Thus, targeting the glutamine pathway in both tumor and stroma resulted in a significant decrease in tumor growth [96]. However, the mechanistic link between CAFs and tumor nutrient demand is not clear. A detailed understanding of these pathways would help in dissecting the actionable targets, including targeting both tumor and TME simultaneously. This approach of simultaneous targeting is limited by the cell-dependent function of different actionable target proteins. These targets are present in both tumor epithelium and TME but possess opposite functions. For example, prostate tumor epithelium-mediated downregulation of p62 in stromal fibroblasts resulted in impaired metabolism through reduced mTOR activity and cMYC expression and release of ROS and IL-6, which in turn enhanced epithelial invasion and tumorigenesis [97]. Therefore, inhibiting their activity in tumor cells could be compensated by increased stromal reactivation.

***ECM*:** Extracellular matrix (ECM) consists of an intricate network of secreted proteins that provide biochemical and mechanical support to different tissues and organs. Tumor cells interact with ECM via transmembrane integrin receptors to control cell migration, proliferation, and metabolism. Tumor relieves anchorage dependence and gets disengaged from the ECM for metastases and dissemination. However, ECM detachment results in impaired glucose uptake, reduced cellular ATP levels, and increased ROS production. Tumor cells endure this stressful environment by altering their nutrient utilization from glycolysis to glutamine-derived TCA metabolism mediated by AMPK-regulated NRF2 expression [98]. Glutamate production through AMPK-mediated glutamine metabolism helps to reduce oxidative stress following anchorage independence. ECM composition and organization are influenced by the presence of CAFs in TME [99]. Higher collagen content has been correlated with altered metabolism in breast cancer due to reduced oxygen and glucose consumption and increased glutamine consumption by tumor cells [100]. In head and neck squamous cell carcinoma (HNSCC), cancer cell-derived glutamate promotes ECM remodeling by maintaining the redox state in CAFs, and aspartate from CAFs sustains cancer cell proliferation [101]. These opposite results

might be due to different tumor types and altered TME composition. ECM undergoes continuous remodeling by expressing a variety of matrix-degrading enzymes, resulting in altered nutrient uptake by the tumor cells. For instance, hyaluronan degradation in ECM enhances transporter GLUT1 mobilization to the plasma membrane and promotes glucose uptake and increased migration of cancer cells [102]. In a nutshell, the studies mentioned above fill a gap in understanding the varying metabolic requirements of cells in anchorage-dependent and -independent conditions. A better understanding of the underlying mechanisms of ECM remodeling and metabolic rewiring in tumors could encourage the development of novel therapeutic interventions.

***Immune cells*:** The hallmarks of TME, including hypoxia, low pH, lactate accretion, waste accumulation, and very high demand for nutrients, create a competitive niche for different cells present in the TME [81, 103]. Multiple studies have demonstrated that this nutrient-competitive milieu favors tumor progression and dampens effector T-cell functions but not necessarily their proliferation [104–106]. Metabolic heterogeneity in the TME plays a key role in the differential intratumoral immune cell recruitment. Metabolic reprogramming by cell-intrinsic and -extrinsic nutrient availability in the TME results in the differential activity of immune cells [107, 108]. Also, tumor cells, by employing the Warburg pathway, limit the nutrient supply to immune cells, thereby inducing the immunosuppression [103]. Increased glycolysis is a hallmark of metabolic alterations of activated immune cells, including macrophages, NK cells, dendritic cells, B cells, and effector T cells [109]. Multiple studies have described T-cell activation by complex metabolic regulation [110, 111]. Earlier studies have shown the association between the differentiation state of T cells (naïve, effector, or memory) and their metabolic activity [112]. Naïve T cells have basal glucose requirements and depend mainly on fatty acid oxidation and glutaminolysis for their nutrient supply, while activated T cells undergo metabolic switching towards glucose metabolism. For T-cell activation, CD28 costimulation promotes glucose uptake via the PI3K-AKT pathway, and TCR activation induces glutaminolysis through ERK/MAPK pathway [113]. Additionally, enhanced mTOR activity results in the activation of CD8+ T cell and stabilization of HIF1α required for CD4+ T-cell proliferation and activation. Effector T-cell subsets, including TH17, TH1, TH2, and activated $CD8^+$ T cells, have been shown to possess high glycolytic activity as seen by increased mTOR activation. Thus, metabolic reprogramming in activated T cells through PI3K-AKT, mTOR, AMPK, and HIF1α signaling pathways gives rise to similar metabolic profiles of both cancer cells and activated T cells [114–116]. This has been one of the major challenges posed by therapeutic interventions directed towards cancer cells.

Glycolysis is important in immune cell programming from TH_{17} to T_{reg} type [117, 118]. The different metabolic requirement of various immune cells is dictated by their functional activity. This is consistent with the idea that CD28 signaling for T-cell activation is dependent on increased glucose uptake while M2 macrophages and T_{regs} can survive in low-glucose conditions as they utilize fatty acid oxidation for nutrient requirement [119, 120]. In fact, switching of T_{reg} metabolic pathway to

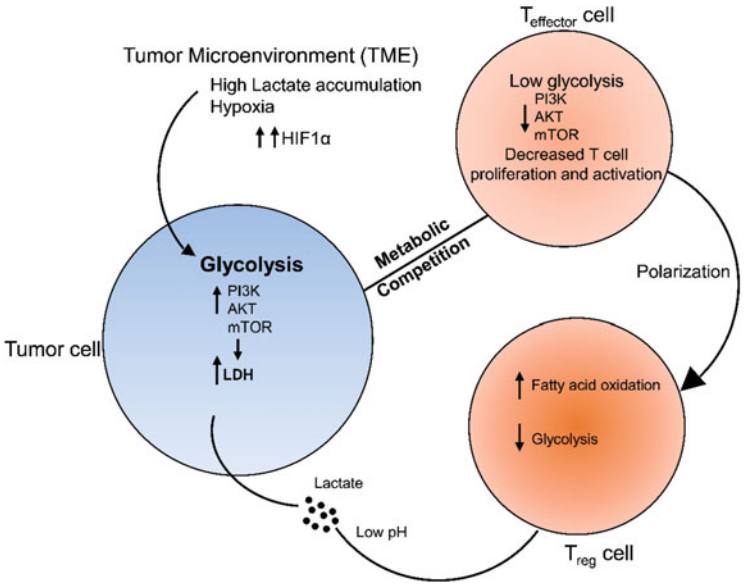

Fig. 2.2 Effect of high lactate accumulation and hypoxia in tumor microenvironment (TME) on T-cell effector function and reprogramming to immunosuppressive Treg cells

fatty acid oxidation may be due to suppression of mTOR by AMPK [81, 121]. Also hypoxia in TME induces high adenosine concentrations by tumor cells; it exerts an immunosuppressive effect through the binding of adenosine receptors in various immune cells [122]. Likewise, lactate accumulation by excessive glycolytic activity in the TME engenders metabolic reprogramming of both tumor and immune cells and angiogenesis through increased VEGF secretion [56, 88]. In one study, excessive lactate accumulation resulted in reduced T-cell effector function and polarization towards T_{reg} phenotype [123, 124] (Fig. 2.2). In addition, reduced activation of infiltrated immune cells (T cell, B cell, and NK cell) and poor monocyte differentiation by excessive lactate concentrations in the TME endow tumor cells with the ability to proliferate at higher levels. While T cells rely solely on glycolysis for their nutrient requirement, hypoxia-induced mitochondrial function loss has also been linked to T-cell exhaustion through MYC-regulated pathway [125]. Nevertheless, there remains a gap in metabolic heterogeneity and its association with immune cell type due to limitations in traditional technologies that help determine the metabolic profile. Recent advancements in flow cytometry and mass spectrometry-based analysis have encouraged researchers to develop innovative approaches of profiling patient samples at a single-cell level. CyTOF-based multiplexing in flow cytometry has allowed single-cell metabolic profiling of human $CD8^+$ T cells in colorectal carcinoma patients [126]. This study suggested that the metabolic heterogeneity in the peripheral and tumor-infiltrating $CD8^+$ T-cell subsets causes differences in their functional attributes. Therefore, delineating the effect of metabolic reprogramming

on tumor immune cell function and distribution will allow intervention with pharmacological inhibitors to remodel the immune response.

2.8 Therapeutic Targeting of Glucose Metabolism

Developing therapeutic strategies targeting the Warburg pathway in tumors has been a long-standing approach to eliminate or delay tumor progression. Several drugs targeting enzymes and intermediates of glycolytic pathways have been evaluated in clinical trials [127] with little success. It is now becoming clear that cancer cells exhibit hybrid metabolism (glycolysis and OXPHOS) under stress conditions induced by the oncogenic activation of Ras, MYC, and c-SRC or ROS generation [128, 129]. Such metabolic plasticity orchestrates the tumor cell proliferation and metastasis by maintaining ROS levels and efficient energy production [45]. In fact, there exist reports indicating the synergistic effect of a combination of glycolytic inhibitor 2-DG decreasing the glucose uptake and metformin inhibiting OXPHOS activity on the growth and metastatic potential of tumor cells [130]. Regardless of the impressive data with 2-DG in several preclinical studies, clinical data are not very satisfactory [131, 132]. A recent clinical trial in PC patients with 2-DG was stopped due to slow accrual. Likewise, clinical trials of other cancers with 2-DG were not satisfactory and unambiguous. Clinical trials combining 2-DG with other chemotherapeutic agents including cisplatin, docetaxel, or radiation are currently ongoing [127]. Data obtained from initial trials are quite encouraging and might open new avenues for cancer treatment. Several other anti-glycolytic agents target different enzymes and intermediates of the glycolytic pathway, including glucose uptake and phosphorylation, fructose phosphorylation, glucotriose metabolism, pyruvate formation, oxidation, lactate dehydrogenase, and tumor acidosis [127]. One of the most effective anti-glycolytic agents, 3-bromopyruvate (3-BrPA), a pyruvate analog, acts by targeting GAPDH and inhibiting both tumor glycolysis and mitochondrial OXPHOS. As a result, cancer cells undergo energy deficiency through ATP diminution and apoptosis and eventually die, leading to decreased tumor growth. In addition, studies have shown the anticancer effect of 3-BrPA through suppressing tumor invasion, angiogenesis, and metastasis. 3-BrPA has shown antitumor potential not only as a single agent but also acting synergistically in combination with cytotoxic agents and ABC transporters to restore drug sensitivity [133, 134]. As 3-BrPA is stable in the acidic TME, it has the potential for efficient tumor cell killing with reduced off-target toxicity. However, nonspecific alkylation by 3-BrPA can induce toxicity in the normal immune and stem cells. Therefore, several attempts are being made for local-regional delivery of 3-BrPA through catheters, microencapsulation, or intra-arterial routes to minimize the toxicity [135, 136]. Likewise, synergistic inhibition of glycolysis and OXPHOS by a combination of metformin with bromodomain and extra-terminal motif (BET) inhibitor, JQ-1, has been tested in pancreatic cancer [137]. These combinatorial targeting strategies could provide ways to overcome therapy resistance and achieve durable responses. The metabolic plasticity of cancer cells in the harsh TME is mediated by a cross talk between

gene regulation and metabolic pathways [1]. A recent study devised a theoretical framework to couple gene signatures and metabolic interplay in the hybrid metabolism phenotype. This study indicated a direct correlation between AMPK and OXPHOS, and HIF1 and glycolysis, highlighting the significance of targeting abnormal metabolism in cancer by modulating both genes and metabolic pathways [41]. The multifaceted interactions between different signaling pathways regulate metabolic reprogramming in cancer cells, allowing them to proliferate and sustain therapeutic resistance. The inhibition of key metabolic regulators, including KRAS, MYC, P53, HIF1α, and PI3K/AKT/mTOR pathways, could be an effective approach towards tumor killing. For instance, targeting KRAS in PDAC patients showed promising results in preclinical studies; however, it had no positive influence on patient survival [17]. Similarly, preclinical studies targeting EGFR and CDK4/6 by afatinib and palbociclib have shown great promise in reducing tumor progression by reducing metabolic reprogramming in HNSCC [138]. Several ongoing preclinical and clinical studies targeting HIF1α, MYC, and P3K/mTOR pathways in various cancers are under progress. Nevertheless, the metabolic plasticity of cancer cells poses a serious therapeutic challenge in targeting a specific pathway as they can overcome the inhibitory effect by activating the alternative metabolic pathways. In addition, other cells of TME, including stroma, fibroblasts, and immune cells, also influence the metabolic milieu of tumor cells and help them survive in a stressful environment. Therefore, current approaches focus on combining anti-glycolytic agents that target different metabolic pathways or their combination with other chemotherapeutic agents to overcome the therapeutic resistance. Overall, the knowledge acquired from these studies will help develop an understanding on future therapeutic perspectives based on metabolic reprogramming.

2.9 Concluding Remarks

Metabolic reprogramming is employed by tumor cells/CSCs to survive and grow in the harsh TME to generate energy and precursors for the biosynthetic process and maintain their redox balance. This reprogramming is achieved by acquiring mutations in the oncogene and tumor-suppressor genes which activates the downstream signaling pathways associated with tumor progression, metastases, and therapy resistance. Apart from metabolic switching from glycolysis to OXPHOS, tumor cells also acquire a hybrid phenotype and utilize both metabolic pathways. While most studies are limited to investigating altered metabolism in tumor cells, a broader understanding of metabolic cooperativity between the tumor cells and stromal compartments may help delineate intricated metabolic pathways and exploit them for novel anticancer therapies.

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