

Accepted Manuscript

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PII: S0304-419X(18)30035-0

DOI: doi:[10.1016/j.bbcan.2018.06.005](https://doi.org/10.1016/j.bbcan.2018.06.005)

Reference: BBACAN 88234

To appear in: *BBA - Reviews on Cancer*

Received date: 2 February 2018

Revised date: 20 June 2018

Accepted date: 20 June 2018

Please cite this article as: Linchong Sun, Caixia Suo, Shi-ting Li, Huafeng Zhang, Ping Gao , Metabolic reprogramming for cancer cells and their microenvironment: Beyond the Warburg Effect. Bbacan (2018), doi:[10.1016/j.bbcan.2018.06.005](https://doi.org/10.1016/j.bbcan.2018.06.005)

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Metabolic reprogramming for cancer cells and their microenvironment: Beyond the Warburg Effect

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Keywords: tumor microenvironment, metabolic reprogramming, biomass synthesis, immune cells, microbiota

ABSTRACT

While metabolic reprogramming of cancer cells has long been considered from the standpoint of how and why cancer cells preferentially utilize glucose via aerobic glycolysis, the so-called Warburg Effect, the progress in the following areas during the past several years has substantially advanced our understanding of the rewired metabolic network in cancer cells that is intertwined with oncogenic signaling. First, in addition to the major nutrient substrates glucose and glutamine, cancer cells have been discovered to utilize a variety of unconventional nutrient sources for survival. Second, the deregulated biomass synthesis is intertwined with cell cycle progression to coordinate the accelerated progression of cancer cells. Third, the reciprocal regulation of cancer cell's metabolic alterations and the microenvironment, involving extensive host immune cells and microbiota, have come into view as critical mechanisms to regulate cancer progression. These and other advances are shaping the current and future paradigm of cancer metabolism.

1. Introduction

For cancer to initiate and progress, cancer cells are thought to need to reprogram their catabolic and anabolic metabolism for energy acquisition and biomass synthesis for cell survival and growth, especially under severe microenvironments [1-3]. Almost a century ago, Otto Warburg observed that cancer cells tended to use glucose avidly via aerobic glycolysis [4, 5]. Over the past two decades, intensive studies in the field have not only established that oncogenic lesions have been largely responsible for the Warburg Effect in cancer cells but also implicated that metabolic reprogramming has evolved far beyond what was originally anticipated [3]. Given the emerging importance of this deregulated metabolism for cancer biology, it appears timely to discuss what we know about cancer metabolic reprogramming that is beyond the Warburg Effect by addressing the following key issues. What are the unconventional energy sources for cancer cells in addition to the major substrates glucose and glutamine? How do cancer cells coordinate anabolic metabolism to satisfy accelerated proliferation? How do cancer cells interact with and educate their microenvironment, especially the immune cells and microbiota, through metabolic rewiring?

2. Unconventional nutrient sources for cancer cells

Glucose and glutamine are two major nutrient sources for cancer cell survival and proliferation because they feed glycolysis and the tricarboxylic acid cycle (TCA). Accompanied by these processes, conventional waste products from cells, such as lactate, acetate, ketone bodies, ammonia and other exogenous proteins, have long been regarded as useless metabolites. Intriguingly, advances in the past several years have identified a variety of new functions in cancer cells for those conventional waste products, which have gradually come to be defined as unconventional nutrient sources for ATP acquisition and for biomass synthesis for building blocks during cancer cells' response to the stressed conditions. Here, we will summarize these unconventional nutrients, highlighting their multiple newly discovered roles for cancer progression (Fig. 1).

2.1. Lactate

Lactate studies date back to the 19th century when Louis Pasteur proposed in 1863 that lactate was produced by the lack of oxygen during muscle contraction, and it has long been considered since the 1920s to be a futile product of aerobic glycolysis in most tumor cells, though lactate produced from active muscle can be utilized by the liver or brain through blood flow for conversion back to glucose via gluconeogenesis under normal physiological conditions, which is known as the Cori cycle [6-8]. Lactate dehydrogenase (LDH), which is commonly induced by oncoproteins such as cMyc, HIF1, and mTOR in cancer cells, reduces the glycolytic end product pyruvate to lactate while simultaneously oxidizing NADH to NAD⁺ [9-11]. Recent studies have expanded the metabolic functions of lactate, supporting cancer cell proliferation as a fuel. For example, in the coculture system of cancer cells and cancer-associated fibroblast (CAF) cells, lactate secreted by CAF cells via monocarboxylate transporter-4 (MCT-4) can be absorbed by cancer cells through MCT-1 to feed mitochondrial oxidative phosphorylation (OXPHOS) for efficient ATP production. In rapidly proliferating HeLa cells and H460 human lung cancer cells, Chen et al. found through metabolic flux analysis via solid-state NMR that ¹³C₃-labeled lactate is metabolized to lipids [8]. Furthermore, they demonstrated that lactate can be imported into mitochondria as a carbon source and metabolized by mitochondrial LDHB for respiration [8].

In 2017, two excellent studies by Hui et al. and Faubert et al. found independently that lactate is the primary carbon source for the mitochondrial TCA cycle in normal tissues and tumors [12-14]. A previous study by Ralph J. DeBerardinis's group found that human non-small cell lung carcinoma (NSCLC) cells exhibit enhanced glycolysis and glucose oxidation relative to adjacent benign lung tissues. They observed that NSCLC tumors can oxidize multiple nutrients, including lactate, as a potential carbon source *in vivo* [15]. Based on this discovery, Faubert et al. went on to study whether lactate contributes to energy metabolism in living tumors and mouse models. Extensively ¹³C-labeled TCA cycle metabolites, such as citrate, glutamate and malate,

are detected when infusing living NSCLC tumors with ^{13}C -lactate, and the inhibition of MCT1 expression in tumor cells eliminates lactate-derived TCA metabolites in mouse models. Furthermore, authors also compared the tracing of [U^{13}C] glucose and [3^{13}C] lactate and found that lactate makes a more prominent contribution to the TCA cycle [13]. Through systematical analysis of turnover fluxes of circulating metabolites in fed mice and fasting mice, the results of Hui et al. showed that the circulatory turnover flux of lactate is the highest and exceeds that of glucose by 1.1-fold and 2.5-fold in fed mice and fasting mice, respectively; further experiments showed that carbon sources from glucose enter the TCA mostly through circulating lactate in almost all tissues both in fed and fasting mice, indicating that circulating lactate in the microenvironment is a major carbon donor to replenish the TCA cycle both in normal tissues and tumors [12] (Fig. 1).

In addition to contributing to TCA cycles, exogenous lactate leads to a concentration-dependent increase in the migration and invasion of cancer cells via the Boyden chamber assay [16], activates multiple oncogenic signaling pathways [17], and positively correlates with radio-resistance [18, 19]. In addition, lactate was also shown to acidify the tumor microenvironment and to shape many immune cells to escape immunosurveillance, which will be discussed in detail in “*part 4.1.1. Glucose Metabolism*”.

2.2. Acetate

While acetyl-CoA is regarded as the sole carbon donor and substrate for both fatty acid and cholesterol biosynthesis and is critical for histone acetylation in mammalian cells [20, 21], many cancer cells are highly glycolytic, and consequently, pyruvate is largely converted to lactate instead of entering mitochondria to yield acetyl-CoA. Thus, the question of which substrate is responsible for the production of acetyl-CoA, especially under nutrient-limited conditions, appears to be particularly important. Cytosolic acetyl-CoA is synthesized through citrate cleavage by ATP citrate lyase (ACLY) or ligation of acetate and CoA via acetyl-CoA synthetase 2 (ACSS2) (Fig. 1). Much is now known about the vital function of the enzyme ACLY and its inhibitors

for cancer cell survival and growth [22-24], but little is known about the detailed role of acetate in cancer development and progression.

Three enzymes catalyze the formation of acetyl-CoA from acetate and CoA: ACSS1, ACSS3, which are located in the mitochondria; and ACSS2, which is located in both the cytosol and nucleus [25-27]. By tracing the incorporation of ¹⁴C-acetate, Comerford and colleagues found that ACSS2 is required for acetate uptake and utilization and that hepatocellular carcinoma development is repressed in ACSS2-deficient mice. Clinical immunohistochemical (IHC) data showed that ACSS2 expression is obviously higher in human breast, ovarian and lung tumor samples than in normal or noncancerous samples [28]. Furthermore, under hypoxic and lipid-depleted (serum-free) conditions, synergistically upregulated ACSS2 contributes to cancer cell growth by partitioning the carbon source into fatty acid and phospholipid pools [29]. In rapidly proliferating and highly malignant glioblastoma tumors, ¹³C-NMR analysis of brain tumors showed that ¹³C-glucose contributes less than 50% of the carbons to the acetyl-CoA pool. Further analysis in mice with primary glioblastomas and brain metastasis indicated that these tumors can oxidize [1,2-¹³C] acetate simultaneously. The same finding was discovered in four patients (two glioblastoma, one breast cancer with brain metastasis, one non-small cell lung cancer with brain metastasis) when infusing [1,2-¹³C] acetate during surgical resection of the tumors [30].

Collectively, these findings reveal the potential role of acetate in the regulation of histone acetylation and biosynthesis of fatty acid and sterol, especially under hypoxic and low lipid conditions. Additionally, ACSS2 was found to be a key enzyme that mediates acetyl-CoA synthesis from acetate, and its expression correlates with tumor aggressiveness in different organs. All these findings suggest that the utilization of acetate may be a general feature of many cancers [31].

2.3. Ketone bodies

Ketone bodies are mainly synthesized from acetyl-CoA in liver mitochondria when the amount of FAO (fatty acid oxidation or β-oxidation)-derived acetyl-CoA

surpasses citrate synthase activity and/or oxaloacetate availability for condensation to form citrate; then, it is transported to extrahepatic tissues such as brain, heart and skeletal muscle, where carbohydrates are in short supply in mammalian cells. This process is called ketogenesis, including a series of enzymatic reactions activated by mitochondrial thiolase (m-thiolase), HMG-CoA synthase 2 (HMGCS2), HMG-CoA lyase (HMGCL) and D- β OHB dehydrogenase (BDH1) with the production of acetoacetate (AcAc), acetone and β -hydroxybutyrate (β -HB) [32].

Ketolysis (ketone body catabolism) begins when AcAc and β -HB are transported to oxidative organs through blood flow, where these two substrates are then metabolized under the supervision of BDH1, succinyl-CoA:3-oxoacid-CoA transferase (OXCT), and m-thiolase to generate acetyl-CoA. Thus, ketone body metabolism is related to the TCA cycle, de novo lipogenesis, sterol biosynthesis, β -oxidation and the mitochondrial electron transport chain, intracellular signal transduction via the generation and consumption of acetyl-CoA [33, 34] (Fig. 1).

When carbohydrates such as glucose is scarce, energy must be obtained from breaking down fatty acids in the human body. For example, the heart can obtain much of its energy from ketone bodies, although it also uses many fatty acids [35]; the brain uses ketone bodies that are able to pass through the blood-brain barrier for energy when glucose is insufficient [36, 37], but hepatocytes lack the ability to catabolize the ketone bodies produced by themselves because expression of the key ketolytic enzyme, OXCT1, is absent or suppressed in adult liver [38, 39]. Our previous study documented that β -oxidation is inhibited in cancer cells to alleviate oxidative stress to promote cell survival under hypoxic stress conditions [40]. Interestingly, our recent study found that OXCT1, the key enzyme for ketolysis, is activated in liver cancer cells. Metabolic flux analysis using the labeled [2,4-¹³C₂] β -HB revealed that ketolysis is reactivated in serum-starved hepatocellular carcinoma cells to facilitate cell survival and proliferation. A mechanistic analysis showed that OXCT1 is induced by the mTORC2-AKT-SP1 signaling pathway under nutrient-limited conditions. By supporting ATP production, OXCT1-mediated ketolysis suppresses AMPK activation and protects liver cancer cells from autophagic cell death. Thus, this study discovered

an unexpected correlation between ketolysis and liver cancer progression, providing evidence for understanding the pathogenic mechanism of liver cancers as well as potential targets for liver cancer therapy [41].

2.4. Ammonia

Free ammonium ions are produced mainly during glutaminolysis, asparagine catabolism, de novo cysteine synthesis, pyrimidine degradation and urea circulation in the human body [42]. Commonly, free ammonium ions are produced by glutaminase (GLS) and glutamate dehydrogenase (GDH) from glutamine and glutamate in mitochondria, respectively, and utilized by glutamine synthetase (GS) to synthesize glutamine [43] (Fig. 1).

Ammonia often accumulates in the tumor microenvironment because of inefficient vascularization, resulting in its accumulation inside tumor cells. The fates and roles of the ammonia released from cancer cells are not fully understood. Potentially a nitrogen donor, it would make more sense if the ammonia could be reused in a metabolic pathway by the cancer cells. In other words, whether cancer cells use nitrogen fixation for biosynthesis like bacteria, yeast and plants is a very fascinating question. In 2016, Yang et al. found that ammonia in the microenvironment can be captured by CAF cells to synthesize glutamine; then, newly synthesized glutamine is secreted to ovarian cancer cells for nucleotide synthesis and TCA cycle metabolite enrichment [44]. More recently, to investigate the fate of ammonia, Spinelli et al. detected the fate of ¹⁵N-glutamine by ¹⁵N tracing in estrogen receptor-positive (ER⁺) breast cancer cells. Unexpectedly, the ¹⁵N isotope is incorporated into proline, aspartate, branched-chain amino acid (BCAAs) and glutamate through ammonia derived from ¹⁵N-glutamine in addition to the expected asparagine and nucleotides. Further mechanistic analysis indicated that GDH is responsible for glutamate formation from ammonia and α -ketoglutarate (α -KG). In vivo, ammonia released into the microenvironment by the liver is absorbed by breast cancer cells, then ammonia and α -KG are utilized by GDH to form glutamate and other BCAAs to promote breast cancer cell growth and proliferation via supporting nitrogen sources [45]. However, in

some studies, GDH was not found to be essential for cell growth [46, 47], and the production of α-KG was not found to be critical for tumor proliferation [48, 49]. Thus, based on the discovered crosstalk between ovarian cancer cells and CAFs, breast cancer cell-autonomous ammonia assimilation [50, 51], it will be interesting to explore the detailed functions of metabolic enzymes and metabolites in different cancer contexts and cell types.

2.5. Exogenous proteins

Almost all cancer cells are addicted to glucose and certain amino acids, but these nutrients will not be enough for cell growth because of the rapid proliferation of tumor cells together with the poor vascularization of tumor tissue. In addition to the metabolites such as lactate, acetate, ketone bodies and ammonia mentioned above, many studies have found that exogenous proteins, living cells and apoptotic bodies can also be absorbed, digested and decomposed by tumor cells to support survival under nutrient-stressed conditions [3].

Under amino acid-deficient conditions, RAS-transformed cells can survive and grow by transporting extracellular proteins into cells, an event termed micropinocytosis. Macropinocytosis is a highly conserved endocytic process that couples with the catabolism of extracellular proteins into free amino acids, including glutamine in lysosomes [52] (Fig. 1). This metabolic manner is also a critical nutrient uptake mode for the growth of human pancreatic cancers with poor vascularization [53]. Later, Palm et al. found that RAS-induced macropinocytosis and lysosomal degradation of extracellular proteins activates the mTORC1 pathway, whereas the mTORC1 pathway inhibits the digestion of extracellular proteins via negative feedback machinery, and thus, mTORC1 inhibitors promote cancer cell growth under amino acid deprivation conditions. This finding indicates that the use of mTORC1 inhibitors as anticancer therapeutics should depend on the environmental nutrient status [54]. Growth factor signaling is also involved in micropinocytosis and lysosomal catabolism of extracellular proteins under limited extracellular amino acid conditions. Palm et al. further found that phosphatidylinositol 3-kinase (PI3-kinase)

signaling is responsible for the use of extracellular proteins as amino acid source under growth factor stimulation. RAS-related C3 botulinum toxin substrate 1 (Rac1), phospholipase C (PLC) and AKT serine/threonine kinase (AKT) are downstream proteins of PI3K signaling, and further analysis revealed that Rac1 and PLC are required for micropinocytosis, whereas AKT suppresses lysosomal catabolism of extracellular proteins and induces the expression of amino acid transporters under nutrient replete conditions. Thus, these findings indicate that PI3K pathway supports cancer cell proliferation by fluctuating nutrient environments with various amino acid sources [55]. Two other methods for amino acid recovery are entosis and phagocytosis, by which cancer cells digest surrounding living cells and apoptotic cells, respectively. Cells engulfed through entosis and phagocytosis will be digested within lysosomes in a method similar to micropinocytosis [56, 57]. In sum, micropinocytosis, entosis and phagocytosis are all opportunistic ways for tumor cells to deal with depleted normal nutrients such as glucose, glutamine and other essential amino acids to acquire growth advantages in atrocious tumor microenvironments.

3. Biomass synthesis and cell proliferation

Cancer cells not only need ATP produced by glycolysis and the TCA cycle for survival but also require biomass synthesis for cell proliferation under both normal and stressed conditions. In tumor cells or tumors *in situ*, especially solid tumors, disruptions of internal organizational structure and insufficient vascularization lead to nutrient exhaustion. Here, we will summarize the latest discoveries regarding the rewired biosynthetic pathways and their underlying regulatory networks, focusing on the pentose phosphate pathway (PPP), serine synthesis pathway (SSP) and branched-chain amino acid (BCAA) metabolism, with an aim to provide new cancer therapeutic insights by targeting these deregulated metabolisms (Fig. 2).

3.1. Pentose phosphate pathway

The pentose phosphate pathway is parallel to and branched from the first rate-limiting step of glucose metabolism. In cells, glucose is phosphorylated to glucose-6-phosphate by hexokinase (HK). Glucose-6-phosphate is at the intersection of three glucose metabolic pathways: glycolysis, glycogen synthesis and the PPP. The PPP provides ribose for the synthesis of nucleotides and is also the major donor of NADPH in maintaining redox homeostasis to promote DNA replication and fatty acid synthesis (Fig. 2).

Recently, an increasing number of studies have focused on the crosstalk between metabolic dysregulation and other hallmarks of cancer, such as cell cycle disorders, pointing to the existence of a complicated network of cell cycle signaling intertwined with metabolic inputs [58-63]. Jiang et al. found that P53, which is the most frequently mutated tumor suppressor gene, inhibits the PPP by repressing glucose-6-phosphate dehydrogenase (G6PD) enzyme activity. TAp73, a structural homologue of p53, activates the PPP and accelerates cell growth by promoting G6PD expression [64, 65]. Cell cycle-related protein cyclin-CDK (cyclin-dependent kinase) complexes are frequently amplified in various cancers, and inhibitors of CDK4 and CDK6 are currently being tested in clinical trials with good efficacy, but the mechanism of these inhibitors is not fully understood. Recently, Wang et al. reported that hyperactivated cyclin D3-CDK6 kinase phosphorylates and inactivates two glycolytic enzymes, 6-phosphofructokinase (PFK) and pyruvate kinase M2 (PKM2), thus redirecting glycolytic intermediates into the PPP and the SSP. Together, all these metabolic alterations result in enhanced NADPH and glutathione (GSH) production, which eliminates reactive oxygen species (ROS) and promotes cancer cell survival [66]. Coinciding with the discovery of the new roles for cyclin D3-CDK6 on metabolism, we recently found that polo-like kinase 1 (PLK1), a G2/M kinase, directly binds to and phosphorylates G6PD, which catalyzes the rate-limiting step of the PPP and is coupled with the production of NADPH. PLK1 phosphorylated G6PD is vital for G6PD dimer formation and its enzyme activity, leading to enhanced production of NADPH, ribulose 5-phosphate (R5P) and nucleotide synthesis, which ultimately promote cancer cell proliferation and tumor progression [67]. These

findings suggest that coordination between the cell cycle and biomass synthesis is critical for cancer progression.

3.2. Serine synthesis pathway

Another glycolytic intermediate, 3-phosphoglycerate (3PG/G3P), is the major entry substrate of the serine synthesis pathway and is metabolized through a series of biochemical reactions by four cytoplasmic enzymes, PHGDH, PSAT1, PSPH, and SHMT1, and one mitochondrial enzyme, SHMT2, into serine and glycine, two nonessential amino acids in mammals. Additionally, glutamate can be converted to serine by PSAT1 and PSPH [68-71]. Apart from their known functions in the central nervous system [72, 73], their roles have been neglected for many years in the study of tumor development and progression, though studies in 1986 indicated that de novo serine synthesis was increased in cancer cells [74]. It is encouraging that the past few years have seen striking involvement of these two amino acids in cancer progression [75-78].

Serine is required for many biosynthetic and signaling pathways and provides one carbon units into the folate cycle through one carbon metabolism along with the production of nucleotides. GSH, a tripeptide that is composed of glycine, glutamate and cysteine, is generated and contributes to the redox balance in cells by scavenging reactive oxygen species [79-82]. Thus, the SSP pathway promotes cancer cell proliferation through providing biomass and maintaining redox homeostasis [71, 75, 83] (Fig. 2). PHGDH is amplified in melanoma and breast cancer. In particular, protein levels of PHGDH are elevated by 70% in estrogen receptor-negative breast cancer cells relative to normal breast tissue [84-87]. Recently, studies of PHGDH inhibitors have become increasingly prevalent. Lewis C. Cantley and colleagues found that CBR-5884, a PHGDH inhibitor identified from an 800,000 drug-like compound library, inhibits the proliferation of cancer cells addicted to serine synthesis based on cell-based assays [88], but the specific binding mechanism of CBR-5884 on PHGDH and its effect in vivo remains unclear. Later, by screening the NIH Molecular Libraries Small Molecule Repository (MLSMR) library, the group of David M.

Sabatini found that NCI-503 compound with a piperazine-1-carbothioamide scaffold suppresses serine synthesis and reduces the incorporation of carbons from both intracellular and extracellular serine into nucleotides by inhibiting PHGDH enzyme activity [89]. To analyze the binding sites of PHGDH inhibitors on PHGDH, Wang et al. found two potential allosteric sites in PHGDH via computational prediction and surface mode illustration. More importantly, two compounds, PKUMDL-WQ-2101 and PKUMDL-WQ-2201, were found to directly bind to these sites, inhibit PHGDH-mediated serine biosynthesis in cell-based assays and suppress tumor growth *in vivo* [90].

Serine was also found to act as an allosteric activator of PKM2, leading to increased PKM2 activity and glycolysis [91, 92], whereas PKM2 activators reduce carbon flow to SSP and induce serine auxotrophy [93]. Upon serine starvation, p53 activates p21 to promote GSH production to combat ROS [94, 95]. Additionally, TAp73, ATF4, G9A, NRF2 and PKC ζ are all reported to regulate serine biosynthesis and metabolism [92, 96-99]. cMyc is well known to regulate up to 10-15% of human genes involved in regulation of the cell cycle, development, apoptosis and metabolism [100-102]. In addition to the regulation of glucose, glutamine and nucleotide metabolism by cMyc [103-105], we found that the metabolism of serine and glycine is also controlled by cMyc under both normal and nutrient deprivation conditions [106]. In hepatocellular carcinoma (HCC) cells, almost all SSP enzymes are directly activated by cMyc at the transcriptional level under nutrition starvation conditions. Activation of SSP leads to elevated GSH levels, nucleotide synthesis and cell cycle progression. PSPH, the rate-limiting enzyme in hepatocellular cancer, is critical for cMyc-mediated cancer progression. Additionally, the expression of PSPH is higher in HCC patients than in adjacent normal tissue, and aberrant PSPH levels predict HCC patient mortality [106]. This finding suggests that PSPH may represent a potential prognostic biomarker for hepatocellular carcinoma.

3.3. Branched-chain amino acids

Branched-chain amino acids (BCAAs) are essential amino acids such as leucine, isoleucine and valine. These three amino acids must be absorbed through dietary BCAA intake or from protein degradation, providing a nitrogen and/or carbon source for cell growth and proliferation. However, the role of BCAAs in cancer cells was largely overlooked until recently. BCAAs are metabolized in cancer cells by cytoplasmic branched-chain aminotransferase (BCAT1) and/or mitochondrial branched-chain aminotransferase (BCAT2) isoenzymes into corresponding branched-chain α -keto acids (BCKAs) by transferring the α -amino group onto α -KG and yielding glutamate. Glutamate serves as an indirect nitrogen source for nucleotide and nonessential amino acid biosynthesis; BCKAs can be further catabolized to produce acetyl-CoA and succinyl-CoA, which serve as carbon sources that feeds into the TCA cycle for energy generation [107, 108] (Fig. 2).

An accumulating body of evidence indicates that BCAT1 is more important for cancer cell growth in different cancer types than BCAT2. In 2013, Tonjes et al. observed high BCAT1 expression in glioblastoma tumors harboring wild-type isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2), which produce high levels of α -KG and less 2-HG [109]. The imbalance of α -KG and 2-HG regulates BCAT1 transcription by modulating the DNA methylation of its promoter [109]. In another report, BCAT1 inhibition suppresses IDH1/2 expression in epithelial ovarian cancer. However, not all tumors depend on BCAA metabolism or BCAT1 overexpression for cell proliferation and cancer progression. Mayers et al. previously discovered elevated plasma BCAAs in early pancreatic ductal adenocarcinoma (PDAC) but not in NSCLC, even when the tumors are driven by the same genetic mutation [110]. Focusing on these two PDAC and NSCLC mouse models both driven by K-RAS activation together with P53 deletion, they discovered that NSCLC tumors actively catabolize free BCAAs into BCKAs that were incorporated into tissue protein, nonessential amino acid and nucleotides as nitrogen donors, whereas PDAC tumors have decreased BCAA metabolism due to suppressed expression of BCAT2 [111]. These two studies indicate that cancer tissue of origin rather than oncogenic mutation determines the different metabolic manners of BCAAs [112-114]. However, another group provided evidence

that genetic mutations such as the chr18q21 chromosomal deletion also influences BCAA metabolism via BCAT2 in PDACs [115]. The chr18q21 chromosomal region contains tumor suppressor SMAD4 and is frequently deleted in human solid tumors, including PDAC. Dey et al. found that mitochondrial oxidative decarboxylase malic enzyme 2 (ME2) is a passenger deletion in PDAC patients, whereas malic enzyme 3 (ME3) enables survival of ME2-deficient cells. In this study, ME3 promotes BCAA metabolism by increasing the expression of BCAT2 for cell growth in this PDAC cancer type [115]. Different from the conventional and predominant metabolic manner mediated by BCAT1 in most cancer types, Hattori et al. recently reported that BCAT1 aminates the BCKA with an amino group from glutamate to form BCAAs in chronic myeloid leukemia (CML). Musashi2 (MSI2), an RNA binding protein, mediates the upregulation of BCAT1 at the posttranscriptional level in CML. Accumulated intracellular BCAA levels, especially leucine, can activate mammalian target of rapamycin (mTOR) via cytosolic leucine sensor proteins and cancer progression [116].

As described above, in-depth studies on BCAA metabolism over the past several years have emphasized the importance of BCAAs in cancer initiation and progression [107]. Several studies have found BCAT1 as a diagnostic and prognostic marker in certain cancer types, but other reports also indicated that the addiction of cancer cells to BCAA metabolism is tissue of origin and genetic mutation-dependent [111]. More studies are needed to precisely evaluate the function of BCAA metabolism in human malignancies with the aim to develop precise treatments for individual cancer patients.

4. Tumor microenvironment stress and metabolic reprogramming

Metabolic reprogramming may not only affect the survival and proliferating signal within cancer cells themselves but also exert influence on the tumor microenvironment. The tumor microenvironment is complicated, including a social microenvironment and physical microenvironment. The social microenvironment is

composed of immune cells, fibroblast cells, endothelial cells, extracellular matrix and microbiota. During tumor initiation and development, all organisms living in the social microenvironment will encounter poor nutrient and oxygen availability, low pH and redox stress, which together constitute the physical microenvironment [117].

Hypoxia is a central characteristic of almost all solid tumors during progression. Glucose-derived pyruvate is converted into acetyl-CoA by pyruvate dehydrogenase (PDH) complex in mitochondria, but hypoxia inhibits this process by upregulating two major targets, LDHA and pyruvate dehydrogenase kinase 1 (PDK1) [118, 119]. Continuously activated glycolytic and LDHA enzymes will lead to lactate accumulation, which results in a low-pH microenvironment during tumor progression. In addition, hypoxia regulates lipid metabolism through HIF-1 α -suppressed fatty acid β -oxidation [40]. Hypoxia signaling is also involved in serine metabolism, as reported recently by the groups of Craig B. Thompson and Gregg L. Semenza [120-124]. Another microenvironment stress cancer cells often encounter is nutrient deficiency. Studies demonstrated that upon nutrient starvation, metabolic reprogramming of tumor cells occurs to harness all available energy to support their own growth. In addition to our discovery of activated SSP and enhanced ketone body utilization under different nutrient starvation conditions discussed above [41, 106], many groups have reported a variety of metabolites with reprogrammed metabolite utilization, including glucose, glutamine, serine and other unappreciated amino acids [97, 125-127]. Since many excellent review articles have provided novel insights in this regard [2, 128], here, we will highlight the latest progress on the reciprocal regulation of tumor cells and immune cells as well as the microbiota at the crossroad of metabolism reprogramming.

4.1. The interplay between tumor cells and immune cells

Immune cells and tumor cells constitute two major cell populations in the tumor microenvironment, and they will encounter similar physical microenvironmental stresses. Thus, it is very interesting to study how these two kinds of cells coexist and

how tumor cells evade immunologic surveillance from the angle of metabolic regulation.

4.1.1. Glucose metabolism

Glucose is the most available nutrient for cancer cells; however, it is also important for the activation, differentiation and function of T cells. T cells kill tumors by antigen recognition. T cell activation relies on the antigen intensity. Stronger activation of T cells needs more nutrients to support its function. In 2013, Chang et al. found that aerobic glycolysis is required for interferon γ (IFN- γ) production in effector T cells but not for their proliferation or survival [129]. Within mouse sarcoma tumor niche, tumor cells and tumor infiltrating CD8 $^{+}$ T lymphocytes compete for glucose. Consequently, tumor cell-mediated high glucose consumption alters T cell metabolism, represses IFN- γ production, and then promotes tumor progression [130]. An intermediate metabolite of glycolysis, phosphoenolpyruvate (PEP), is found to be necessary for maximal Ca2 $^{+}$ -NFAT (nuclear factor of activated T cells) signaling in infiltrating CD4 $^{+}$ T cells. Hence, enrichment of PEP by overexpressing phosphoenolpyruvate carboxykinase 1 (PCK1) in CD4 $^{+}$ T cells can increase its tumor killing ability [131] (Fig. 3).

Additionally, lactate is secreted into the tumor microenvironment by proliferating cancer cells with a high consumption of extracellular glucose. Two papers published by Kreutz's group found that tumor-derived lactate accumulation is an important factor that represses the activation of dendritic cells and T cells [132, 133]. Later, lactate was found to inhibit monocyte migration and cytokine release and to promote the polarization of resident macrophage to the tumor-associated macrophage 2 (TAM2) phenotype, which results in arginase 1 upregulation, tumor progression and immune escape [16, 134-136]. Recently, Kreutz's group further studied the role and mechanism of lactate in a metastatic melanoma model with a high Warburg phenotype; they found that LDHA-associated lactate production diminishes NFAT levels and dampens IFN- γ production of T cells and NK cells, thus promoting immune escape and melanoma progression [137] (Fig. 3).

4.1.2. Lipid metabolism

Lipid metabolites such as cholesterol and prostaglandin E2 (PGE2) are extensively involved in the activation and function of immune cells [138]. Cholesterol incorporated into the plasma membrane promotes T cell receptor (TCR) signaling and cytotoxic lymphocyte function of CD8⁺ T cells. Xu and colleagues revealed that T cells accelerate cholesterol synthesis via increased transcriptional activity of sterol regulatory element-binding protein (SREBP) upon antigen stimulation [139]. De novo synthesized cholesterol is transported to the plasma membrane or is esterified by acyl-CoA cholesterol acyl transferase (ACAT) in the endoplasmic reticulum (ER) to be stored in lipid droplets. However, when cholesterol is excessive in the ER, it will inhibit SREBP function and reduce the synthesis and import of cholesterol. Therefore, through the inhibition of the activity or genetic deletion of ACAT in CD8⁺ T cells, the authors found upregulated SREBP transcriptional activity, increased cholesterol levels in the plasma membrane and enhanced antitumor function of CD8⁺ T cells. Altogether, this study provides key insight into the function of cholesterol metabolism on the immune response of T cells as well as advice for clinical workers on how to modulate sterol metabolism to improve immune responses [139-141]. PGE2, the end product of arachidonic acid metabolism, is reported to participate in many processes of the immune response by inhibiting immunity and inducing tumor-promoting inflammation. However, the underlying mechanism of how PGE2 affects cancer development is unclear. Recently, Zelenay et al. found that induced PGE2 production by cyclooxygenase 2 (COX2) and prostaglandin E synthase (PTGES) in tumors inhibits type I IFNs and activates IL-6, CXCL1, and G-CSF secretion [142]. By utilizing the nonselective COX inhibitor aspirin or the selective COX-2 inhibitor celecoxib, the authors reported that these COX inhibitors facilitate anti-PD-1-mediated antitumor responses in mouse models with melanoma or colorectal cancer [142-144] (Fig. 3). Recently, the vital role of fatty acid catabolism to preserve the effector function of CD8⁺ T cells was observed under no glucose and no oxygen conditions. PPAR- α , as an upstream regulator, was found to control this

metabolic reprogramming and its agonist could repress tumor growth, especially with the combination of PD-1 blockade [145].

4.1.3. Arginine metabolism

Arginine is a nonessential amino acid that participates in a number of processes due to its endogenous synthesis from the amino acid citrulline, but it is also considered as a semiessential amino acid in pathological conditions such as trauma, sepsis, and cancer [146, 147]. Arginine can be metabolized by nitric oxide synthase (NOS), arginase (ARG), arginine:glycine amidinotransferase (AGAT) and arginine decarboxylase (ADC) enzymes into nitric oxide (NO), ornithine, creatine and agmatine, respectively. Then, these metabolites are involved in nitrogen balance, the urea cycle, protein translation, and the synthesis of polyamine and proline, which sustain the rapid proliferation of cancer cells [148, 149].

Within the tumor microenvironment, iNOS/NOS2 and arginase 1 are two major enzymes involved in arginine catabolism, especially in tumor-associated macrophages (TAMs). TAMs are mainly divided into M1 and M2 TAM subtypes, which differ in the utilization of arginine [148, 150]. Basically, M1 TAMs express iNOS induced by pro-inflammatory cytokines such as IFN- γ , tumor necrosis factor α (TNF α), interleukin 1 beta (IL-1 β) and bacterial lipopolysaccharide (LPS); activated iNOS can metabolize arginine to produce NO, which is cytotoxic for tumor cells, whereas M2 TAMs express arginase 1, which is activated by cytokines IL-4 and IL-13 and converts arginine to ornithine, which is a precursor for polyamine synthesis that promotes M2 TAMs polarization and excites surrounding cancer cells [148] (Fig. 3). Recently, Geiger et al. demonstrated that intracellular arginine abundance plays vital roles for the switch from glycolysis to oxidative metabolism in activated T cells. Elevated intracellular arginine levels promote T cell survival, limit T cell differentiation and maintain memory-like T cells, enhancing antitumor activity [151]. Myeloid-derived suppressor cells (MDSCs) are one of the major components of the tumor microenvironment, and their leading feature is immune suppressive activity. MDSCs with expressed arginase reduce extracellular arginine, thus inhibiting the

antitumor function of T cells [152-154]. In contrast, arginase 1 inhibitors suppress MDSC suppressive activity and recover the antitumor function of T cells in a dose-dependent mechanism [152, 155].

Additionally, accruing evidence indicates that tumors educate the microenvironment by depleting essential nutrients and producing immunosuppressive metabolites. Thus, arginine deprivation has been a potential therapeutic strategy for several solid and hematological malignancies lacking arginine-catabolizing enzymes. However, another study indicated that the addition of arginine into mouse breast cancer models could inhibit tumor growth and prolong host survival via enhancing innate and adaptive immune responses [156]. Thus, whether supplementation or deprivation of arginine should be pursued in cancer patients is still uncertain because of the importance of arginine both for cancer cell proliferation and immune cell function.

4.1.4. Tryptophan metabolism

The catabolism of another essential amino acid, tryptophan, has been reported to be characteristic for various tumors, including glioma, breast cancer, lung cancer and colorectal cancer, with higher expression of tryptophan-2,3-dioxygenase (TDO) [157, 158]. TDO is one of the two dioxygenases responsible for the conversion of tryptophan to its derivative kynurene and that exist in cells without indoleamine-2,3-dioxygenase (IDO), another dioxygenase expressed in many types of tumor cells (Fig. 3). Lee et al. and Friberg et al. have found that tryptophan depletion inhibits T cell proliferation, and IDO1-induced tryptophan depletion of the microenvironment facilitates tumor evasion under immune surveillance [159, 160]. Tryptophan catabolism of cancer cells modulates immune cell function mainly through two pathways. First, enhanced tryptophan catabolism of tumor cells depletes extracellular tryptophan and triggers effector T cell (Teff) anergy and renders them more sensitive to apoptotic stimuli [161]. Second, accumulated kynurene and other potential catabolic metabolites are endogenous ligands for aryl hydrocarbon receptor (AHR), a transcription factor that broadly modulates immunity [162]. The activation

of AHR by kynurenine can induce forkhead box p3 (Foxp3) expression in naïve T cells and prevent Th17 maturation, causing proliferation of regulatory T cells (Tregs) [163]. As such, kynurenine promotes the Treg phenotype, inhibits effector T cell function, induces the degradation of extracellular matrix and stimulates invasion.

4.1.5. Metabolism of other amino acids

Mounting evidence indicates that the metabolism of other amino acids is also altered in immune cells. Adequate glutamine is found to be important for the induction of M2 macrophage polarization in response to IL-4 stimulation, but it is not required for M1 macrophage development stimulated by LPS [164]. Activated T cells and B cells are found to possess increased glutamine uptake, and glutamine metabolism is critical for controlling ROS levels and for maintaining the balance between Teff cells and Treg cells [165-167]. Two studies recently reported that serine metabolism-related enzymes and mitochondrial one-carbon metabolism are both induced upon T cell activation. Both serine and mitochondrial one-carbon metabolism are required for T cell survival and proliferation through supporting de novo nucleotide synthesis [168, 169]. Balmer et al. also found that memory CD8⁺ T cells can utilize acetate and augment their acetyl-CoA pool during acute infections [170].

In sum, these studies from independent groups provide remarkable evidence that cancer cells educate their microenvironment by rewiring all available metabolisms in order to evade immunosurveillance of T cells [171-173]. No doubt, other nutrient sources may also potentially participate in these complicated but meaningful processes, which warrant further investigation. Immunotherapy based on these preclinical results need to be further explored in the context of future clinical trials from a therapeutic standpoint.

4.2. The interplay between tumor cells and microbiota and their implication for immunotherapy

The microbiota that colonizes the human body consists of bacteria, viruses, parasites and fungi that live within and on all surfaces of the skin, nose, mouth, stomach, intestine, respiratory tract and urogenital tract [174, 175]. For a long time, the microbiota has been neglected for its important roles in achieving and maintaining the homeostasis of physiological and pathological processes. However, the link between cancer and microorganisms was established through a tremendous amount of research in the past two decades, and, as such, up to 20% of global cancers are deemed to be stimulated by microbial agents [176]. In addition, more and more evidence indicates that microbial presence and activity modulates many host processes, including the metabolic system, immune responses, nervous system, organ development as well as cancer progression.

The microbiota has been reported to be involved in various cancers, including pancreatic cancer, gastric carcinoma and colon cancer, and 50% of plasma metabolites are estimated to have a bacterial origin [177-180]. Based on this result, recent studies have shown the significance of metabolism in understanding how the microbiota affects cancer progression and immune responses. Here, we will summarize the new development of the main products contributed by the microbiota, such as short-chain fatty acids (SCFA), bile acids, polyamines, choline metabolites, indole derivatives and vitamins on cancer progression and the relationship between the gut microbiota and immunotherapy that is connected via metabolites (Fig. 3).

4.2.1. Short-chain fatty acid

Nondigestible dietary fibers are abundant substrates for anaerobic bacterial fermentation in the colon, and their main products are SCFAs, including acetate, propionate and butyrate [175, 181, 182]. As mentioned above in “part 2.2. Acetate”, acetate, as an unconventional nutrient, can be utilized by several human cancers with higher ACSS2 expression, including glioblastoma, breast cancer, ovarian cancer and lung cancer [28-31], but the origin of acetate is unclear. Among the SCFAs, acetate is the only one with a high concentration in the systemic circulation of humans and rodents and makes up more than half of total SCFAs detected in the feces [183, 184].

The gut microbiota is found to be the major source responsible for the increase in endogenous acetate production [183]; perhaps this can partially explain how acetate accumulation occurs in many cancer types. Recently, Perry and colleagues found that accumulated acetate produced by the gut microbiota activates the parasympathetic nervous system, which in turn, promotes glucose-stimulated insulin secretion, obesity and related metabolic syndrome, such as fatty liver disease and insulin resistance [183]. These results together indicate the role of acetate generated by the gut microbiota in the promotion of cancer initiation and progression.

In contrast to acetate, two other SCFAs, butyrate and propionate, mainly exert oncosuppressive roles during cancer progression as inhibitors of histone deacetylases (HDACs) or as ligands for G protein-coupled receptors (GPCRs), such as GPR41 and GPR43 (also known as free fatty acid receptor 2/FFA2), in a context-dependent manner [185-187]. The suppressive effects of butyrate on the development of colorectal cancer (CRC) via promoting colon motility, visceral irrigation, apoptosis; and reducing inflammation and inhibiting tumor cell progression have been the main foci of butyrate research in cancer studies [188-191]. Butyrate induces apoptosis of CRC cells as an inhibitor of HDACs, and the protective role of dietary fiber on CRC progression is dependent on butyrate produced by the gut microbiota in animal studies [192]. In addition, several studies in humans reveal that butyrate-producing bacteria are decreased in CRC patients compared with healthy controls [193]. Butyrate derived from the gut microbiota can deplete oxygen and activate the HIF1 signaling pathway, which plays a barrier-protective role in the distal gut mucosa [194, 195]. Moreover, metabolomics analysis discovered that increased fecal concentration of butyrate and propionate in the diet decreases the risk of cancer [196]. Butyrate and propionate also induce differentiation of Treg cells, assist in the control of intestinal inflammation and reduce the risk of inflammatory bowel disease (IBD) and CRC through maintenance of the gut mucosal barrier [192, 197]. Inulin-type fructan (ITF)-derived propionate was reported to reduce hepatic cancer cell proliferation by activating GPR43 [198].

Nevertheless, the role of propionate is not as well known as those of two other SCFAs, especially that of acetate, and even less known is the role of SCFAs other

than these three. It might be beneficial to investigate whether increasing colonic butyrate or decreasing acetate production could prevent or treat CRCs or other human malignancies.

4.2.2. *Bile acids*

Bile acids are critical components of the enterohepatic circulation that links the gut microbiota, liver metabolism and intestinal metabolism and that, therefore, affects the development and progression of gastrointestinal cancers, including CRC and HCC [199]. Bile acids are mainly produced in the liver by cytochrome P450 (CYP)-mediated oxidation of cholesterol and are secreted into intestinal tract, where they are metabolized by enzymes derived from intestinal bacteria [200, 201], and finally, bile acids are reabsorbed in the intestine and transported back to the liver to complete the so-called enterohepatic circulation [202]. The main functions of bile acids are to maintain healthy microbiota to facilitate the metabolism of dietary fat. Primary bile acids (such as chenodeoxycholic acid/CDCA and cholic acid/CA) are conjugated with taurine (primarily in mice) and glycine (mainly in humans) to form bile salts in the liver, and these bile salts are deconjugated by anaerobic bacteria of the genera *Bacteroides*, *Eubacterium*, and *Clostridium* through the action of bile salt hydrolase (BSH) in the intestine [203]. Then, intestinal bacteria, including *Bacteroides*, *Eubacterium*, *Clostridium*, *Lactobacillus* and *Escherichia*, further convert deconjugated primary bile acids into secondary bile acids (such as lithocholic acid/LCA and deoxycholic acid/DCA) via 7 α -dehydroxylation by cholesterol 7 α -hydroxylase (CYP7A1) [202].

Unconjugated bile acids are endogenous ligands for the nuclear farnesoid X receptor (FXR) [204], pregnane X receptor (PXR) [205], constitutive androstane receptor (CAR) [205], vitamin D receptor (VDR) [206], and G protein-coupled bile acid receptor 1 (TGR5) [207, 208]. Thus, bile acids can influence host and gut microbiotic metabolism by binding to these ligand-activated transcription factors. Mounting evidence indicates that high concentrations of secondary bile acids have potential DNA-damaging functions and are associated with inflammation and disease

development such as HCC and CRC. DCA, LCA or CDCA have been independently reported to have cytotoxic and cancer promoting functions [209, 210]. Yoshimoto et al. discovered an imbalance of the gut microbiota and increased hepatic DCA levels in mice with HFD treatment [211, 212]. High-level DCA in the liver leads to senescence-associated secretory phenotype (SASP) and induces the secretion of various inflammatory and tumor-promoting factors that promote the development of obesity-associated HCC in mice after exposure to a chemical carcinogen, DMBA (7,12-dimethylbenz(a)anthracene) [212]. DCA has also been reported to promote the development of colon cancer and esophageal adenocarcinoma (EAC) in the context of obesity [213, 214]. Clinical patients with fatty liver disease or HCC often possess increased bacteria, such as *Clostridium*, which are capable of generating secondary bile acids [202]. These microbiota-induced variations in bile acids and components might, therefore, inhibit FXR function and a series of signaling transduction pathways related to HCC progression, so either a low-fat diet or pharmacological inhibition of the microbial conversion of primary to secondary bile acids may reverse this phenomenon [215, 216]. In addition to the influence on hepatic cells, secondary bile acids directly or indirectly affect colonic epithelium and the initiation and development of colon tumorigenesis by inducing DNA oxidative damage, activating β -catenin, NF- κ B signaling and p53 degradation, binding to FXR, impairing mitotic activities and cell proliferation [214, 217, 218]. CA, DCA and LCA promote CRC formation by a direct proliferative effect on undifferentiated mucosal epithelial cells [219-223]. A recent study revealed that increased bile acid levels induce the activation of the NF- κ B pathway and promote the release of arachidonic acid, which is metabolized into PGE2, another oncometabolite, thus facilitating CRC formation [224]. Bile acids bind to nuclear receptor FXR, which in turn transcriptionally regulates the bile acid signaling pathway by maintaining bile acid concentrations within a physiological range and by preventing bile acid-induced cytotoxicity [225, 226]. The results of many cellular and mouse model studies have indicated that FXR expression is negatively related to CRC progression, and indeed, in mice deficient in FXR, increased bile acids are observed with pro-tumorigenic roles [227].

4.2.3. Polyamines

Polyamines (PAs) are present in all living cells of mammalian species and are mainly synthesized from arginine or from exogenous food stuff digested by the gut microbiota in the intestinal tract, which contains high levels of polyamines. As mentioned above in arginine metabolism, polyamine precursor ornithine, which is derived from arginine, is metabolized by ornithine decarboxylase (ODC) into putrescine (PUT), which further generates spermidine (SPD) and spermine (SPM) by sequential enzymes spermidine synthase (SRM) and spermine synthase (SMS) [228]. The functions of polyamines are various, including synthesis and stabilization of DNA, RNA and proteins; gene transcription and translation; and stimulation of cell proliferation and differentiation.

Since the first discovery of polyamines in 1678 by Van Leeuwenhoek, many studies have revealed that polyamines affect numerous processes of tumorigenesis [229]. Increased polyamines promote cell proliferation, suppress apoptosis and induce gene expression, which is involved in tumor migration and invasion [230, 231]. In addition, the expression and activity of metabolic enzymes involved in polyamine biosynthesis, such as ODC, is higher in cancerous tissues than in adjacent normal tissues, which suggests that activated polyamine biosynthesis is important for the proliferation and malignancy of most cancer cells [232-237]. Polyamine levels are often increased in the blood and urine of cancer patients, and this phenomenon has been shown to correlate with poor prognosis [238]. Furthermore, the substrate analogue difluoromethylornithine (DFMO) is a specific inhibitor that irreversibly inactivates ODC activity and that has been widely studied in animal models for its suppression of tumor progression [239]. Reductions in polyamine through the inhibition of ODC activity could suppress tumor growth in a T cell-dependent manner, indicating that the intratumoural availability of polyamines protects the immunosuppressive microenvironment [240, 241]. In addition, polyamines could affect the efficacy of target therapies. For example, mutant BRAF (BRAF^{V600E}) melanoma cells are found to be resistant to the BRAF inhibitor, PLX4720, by

adapting to oxidative metabolism in certain conditions [242, 243]; however, co-treatment with polyamine transport inhibitor, arylmethyl-polyamine (AP) compound, would render these cells more sensitive to BRAF inhibitors [244]. Recently, through mass spectrometry-based metabolomics analysis, researchers observed higher concentrations of polyamine metabolites such as SPD, SPM and N^1,N^{12} -diacetylpbermane (DAS) in surgically resected cancer tissues from colon cancer patients. Further analysis indicated that increased polyamines create oncogenic transformation conditions for colon cells [245, 246].

However, other studies have revealed beneficial effects of polyamines for different species. Two papers by Eisenberg et al. found that the natural polyamine spermidine inhibits oxidative stress in aging mice, triggers histone H3 deacetylation and suppresses oxidative stress and necrosis in aging yeast. By suppressing the activity of EP300 acetyltransferase, spermidine promotes autophagy, a cellular process that degrades and recycles old components of the cell and toxic products, and extends the lifespans of yeast, flies, worms and human cells [247]. In addition, dietary supplementation of mice with spermidine decreases the risk of cardiovascular disease (CVD) and death upon aging through an enhancement of autophagy protein 5 (Atg5)-dependent cardiac autophagy, mitophagy and mitochondrial respiration. Similar effects of spermidine on humans are obtained from lower incidence of cardiovascular disease of humans supplied with high levels of dietary spermidine [248, 249]. Matsumoto and colleagues also found that the probiotic strain *Bifidobacterium animalis* subsp. *lactis* LKM512 can enhance mouse longevity through upregulation of the concentrations of intestinal luminal polyamines [250]. Researchers from the same group also found that arginine intake by oral administration increased the concentration of PUT in the colon and SPD and SPM in the blood. Long-term oral arginine uptake combined with LKM512 treatment showed suppressed inflammation, improved longevity, and protection effect from aging-induced memory impairment [251].

Currently, a large number of studies are focused on the roles of polyamines in cancer progression [237], but different groups with various research contexts have

found conflicting effects of polyamines on human health [247, 252, 253]. Additionally, the treatment of colon cancer models and clinical trials with polyamine-metabolism inhibitors have also resulted in ambiguous findings [254]; thus, there is a long way to go to find more successful strategies to target cancer progression by manipulating polyamine contents, such as the issue facing arginine utilization discussed in “part 4.1.3. Arginine metabolism”, in the context of the tumor microenvironment, including cancer cells, microbiota and immune cells.

4.2.4. Gut microbiota and immunotherapy

Immunotherapy, known as checkpoint blockade, is designed to release the antitumor immunity of the host by blocking inhibitory signals expressed on T cells, which can be used by tumor cells to switch off immune cells [255]. Several antibodies targeting these important inhibitory receptors on T cells, including cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and programmed cell death 1 (PD-1), have been approved by the U.S. Food and Drug Administration. Ipilimumab (anti-CTLA-4) and pembrolizumab, nivolumab (anti-PD1) have been applied to treat advanced melanoma and lung cancers clinically [256]. However, only approximately 25% of patients responded to PD-1 blockade and obtained remarkable efficacy in keeping certain cancers at bay for years [257] (Fig. 3). Therefore, immunologists have been evaluating whether a microbiota-host interaction is behind this lower curative effect.

Studies have shown that gut commensals modulate the antitumor efficacy of chemotherapies such as phosphamide and oxaliplatin in mouse models, both of which rely on the activation of antitumor immunity for their tumor killing effect [258-261]. For example: two bacterial species, *Enterococcus hirae* and *Barnesiella intestinihominis*, potentiate the antitumor effect of cyclophosphamide [260, 262]. Furthermore, scientists found that bacteria can also modulate the antitumor function of immunotherapies and reported that the gut microbiota actuates antitumor immune responses and decorates tumor cell’s response to the immune checkpoint blockade in

two papers published in Science in 2015 [263-266]. To investigate whether the gut microbiota influences the immune checkpoint blockade, Sivan et al. compared the growth state of melanoma cells subcutaneously injected into syngeneic C57BL/6 mice with different facilities from either Jackson Laboratories (JAX) or Taconic Farms (TAC) that are known to harbor distinct microbiota. Interestingly, tumors with lower growth rates in JAX mice showed higher CD8⁺ T cell and IFN- γ production. JAX mouse fecal transplant into TAC mice reduces tumor growth and alters dendritic cell activity, which, in turn, leads to increased CD8⁺ T infiltration. Further investigation uncovered that *Bifidobacterium* species are remarkably associated with a CD8⁺ T cell-mediated antitumor immune response [263]. Vétizou and colleagues from Laurence Zitvogel's group reported that anti-CTLA-4 therapy is effective in mice that harbor melanoma that are housed in specific pathogen-free (SPF) conditions but not in germ-free (GF) conditions or under antibiotic (ampicillin, colistin and streptomycin) treatment conditions. Intriguingly, when mice under the latter two conditions are fed with isolated and verified *Bacteroides* that are responsible for the function of anti-CTLA-4, the antitumor role of anti-CTLA-4 is restored [264].

The above studies mainly focused on the interactions between the gut microbiota and immunotherapies in mouse models, but how the gut microbiota shapes the immune responses of human patients to immune checkpoint blockades is largely unknown. Recently, three outstanding groups offered evidence on how bacteria influence the tumor microenvironment and synergize with immunotherapies within human patients [267-270]. Based on the observation in 2015, Zitvogel's group further studied the role of anti-PD-1 treatment in 249 patients with lung cancer, renal cell carcinoma and bladder cancer; 69 patients among these 249 individuals accepted antibiotic treatment for different reasons, but the results showed that patients under antibiotic treatment possessed disturbed microbiota and relapsed sooner, accompanied by a shorter survival due to the negative response to anti-PD-1 treatment. Through analysis of the fecal microbiota between positively and negatively responding patients, the authors found that increased *Akkermansia muciniphila* in responsive patients showed beneficial outcomes to PD-1 drug treatment [267]. Gopalakrishnan et al.

surveyed the variation of gut microbiota of patients with metastatic melanoma under treatment with anti-PD-1 antibody and discovered that the *Faecalibacterium* genus has a higher response by boosting CD8⁺ T cells [268]. Through the analysis of similar patients with metastatic melanoma undergoing anti-PD-1 therapy, Matson et al. discovered that 5 of 8 microbial species enriched in the intestines improve the efficacy of anti-PD-1 therapy via FMT assay (fecal microbiota transplantation), including the *Bifidobacterium* species mentioned above by Sivan et al. in 2015 from the same group of Thomas F. Gajewski [263, 269]. There are no universal bacterial species that respond to anti-PD-1 therapy, although all these studies consistently show the critical roles of gut microbiota in immunotherapies [267-269]. The reasons may be because of the diversity of cancer types compared the surveys of Zitvogel's group with the other two groups, but it is still unclear why different bacteria species respond to the patients with metastatic melanoma studied by Gopalakrishnan et al. and Matson et al. A detailed study of the mechanism by integrating the tumor immune microenvironment; the dose, frequency and timing of immune checkpoint blockade; and metabolic dysregulation may open the window of precise immunotherapies for individual patients with different cancer types.

All results and viewpoints from the studies mentioned above suggest that microbiota should be considered when evaluating the therapeutic effects of immunotherapies both in mouse models and clinical patients due to individual differences, distinct living environments, different dietary habits and antibiotic exposure [270, 271]. Therefore, it is time to carry out large-scale clinical trials to investigate how the gut microbiota shapes the outcome of patients' responses to immunotherapy in detail, though it seems to be difficult and complicated.

5. Closing remarks

Over the past two decades, the understanding of metabolic alterations in cancer cells has advanced far beyond the originally described Warburg Effect. As a consequence, scientists are able to appreciate more comprehensively the mechanisms

behind the survival and growth advantages for cancer cells that are associated with metabolic reprogramming. These advances may be explored therapeutically for treating patients with various malignancies as multiple strategies targeting cancer-specific metabolic alterations such as IDH1, IDH2, LDHA, PDK1, GLS1 have already demonstrated great promises in animal models or clinical trials [1-3]. It is potentially very promising to target cancer by blockading its unique ability to utilize unconventional nutrient sources, as those abilities are very specific for the growth and survival of cancer cells. More importantly, it is urgent to explore the interaction between cancer cell's metabolic alterations and host immune cells or microbiota for cell therapies that may lead to synthetic lethality.

Conflict of interest

The authors declare no conflicts of interest.

Transparency Document

The <http://dx.doi.org/10.1016/j.bbcan.2018.xx.xxx> associated with this article can be found in the online version.

Acknowledgements

Our primary work is supported in part by National Basic Key Research Program of China (2014CB910600), National Key R&D Program of China (2017YFA0205600), National Natural Science Foundation of China (31571472, 81530076, 81525022 and 81702361) and the Program for Guangdong Introducing Innovative and Entrepreneurial Teams (2017ZT07S054)

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Fig. 1. Unconventional nutrient sources for cancer cells

Fig. 2. Deregulated biomass synthesis pathways for cancer progression

Fig. 3. Metabolic connections between tumor cells, immune cells and microbiota under the tumor microenvironment

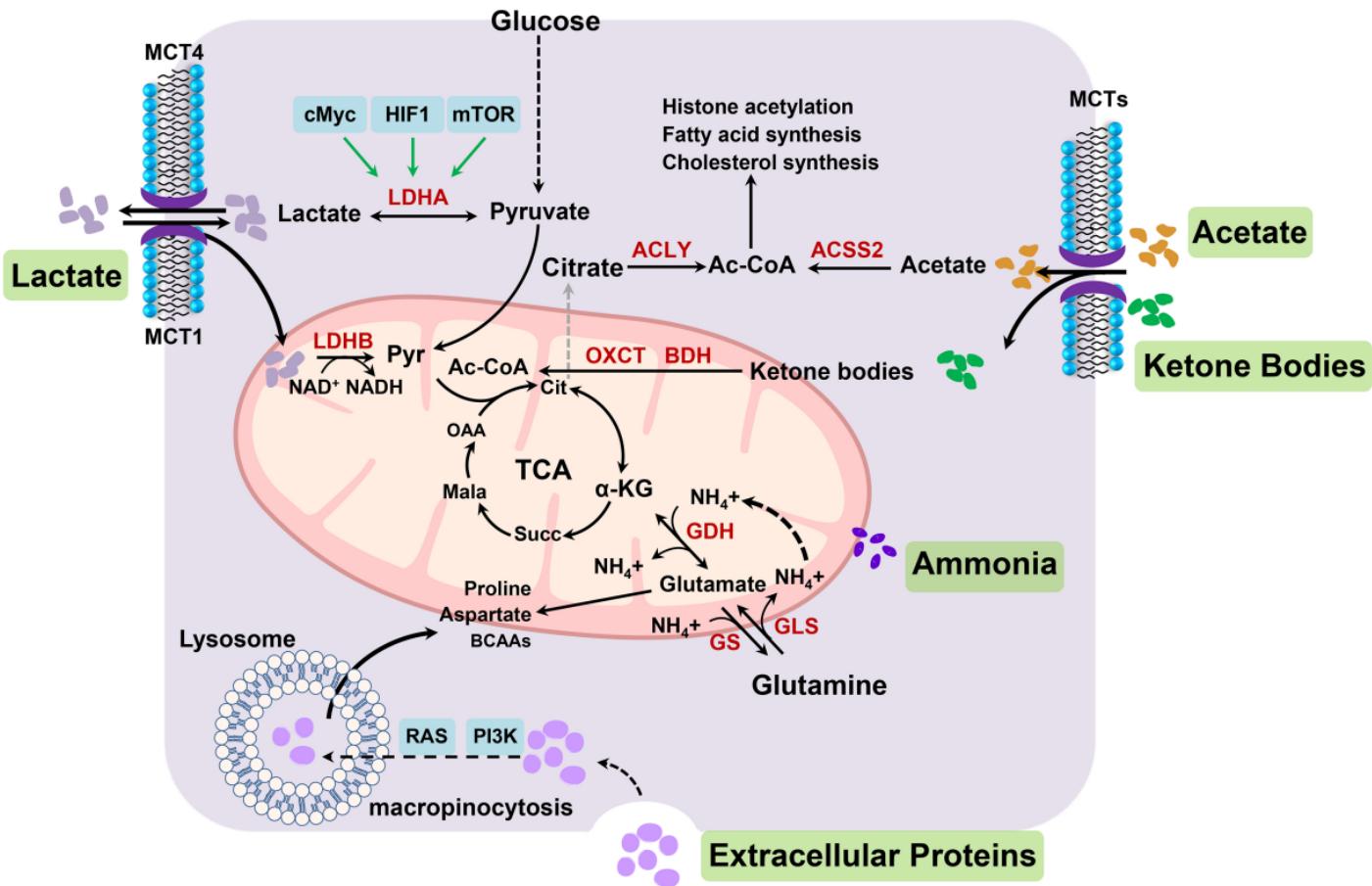


Figure 1

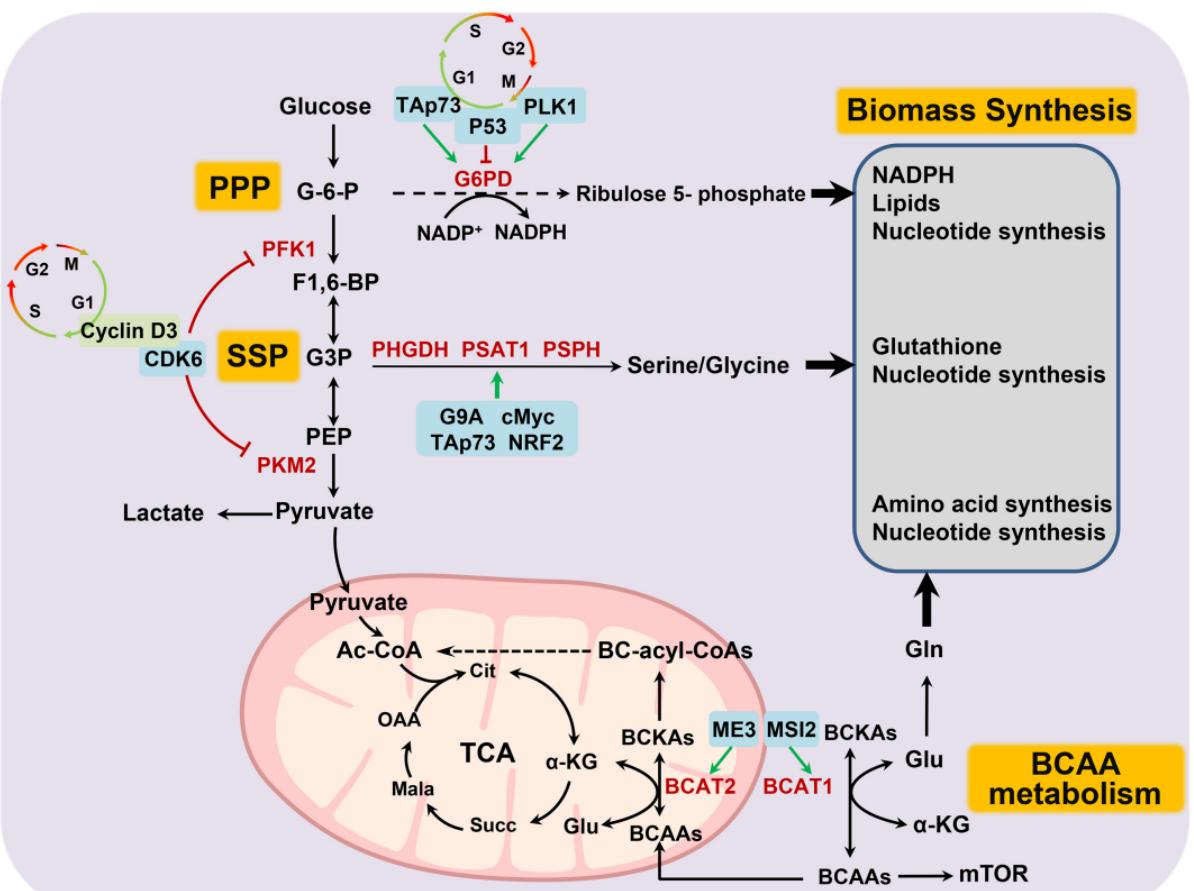


Figure 2

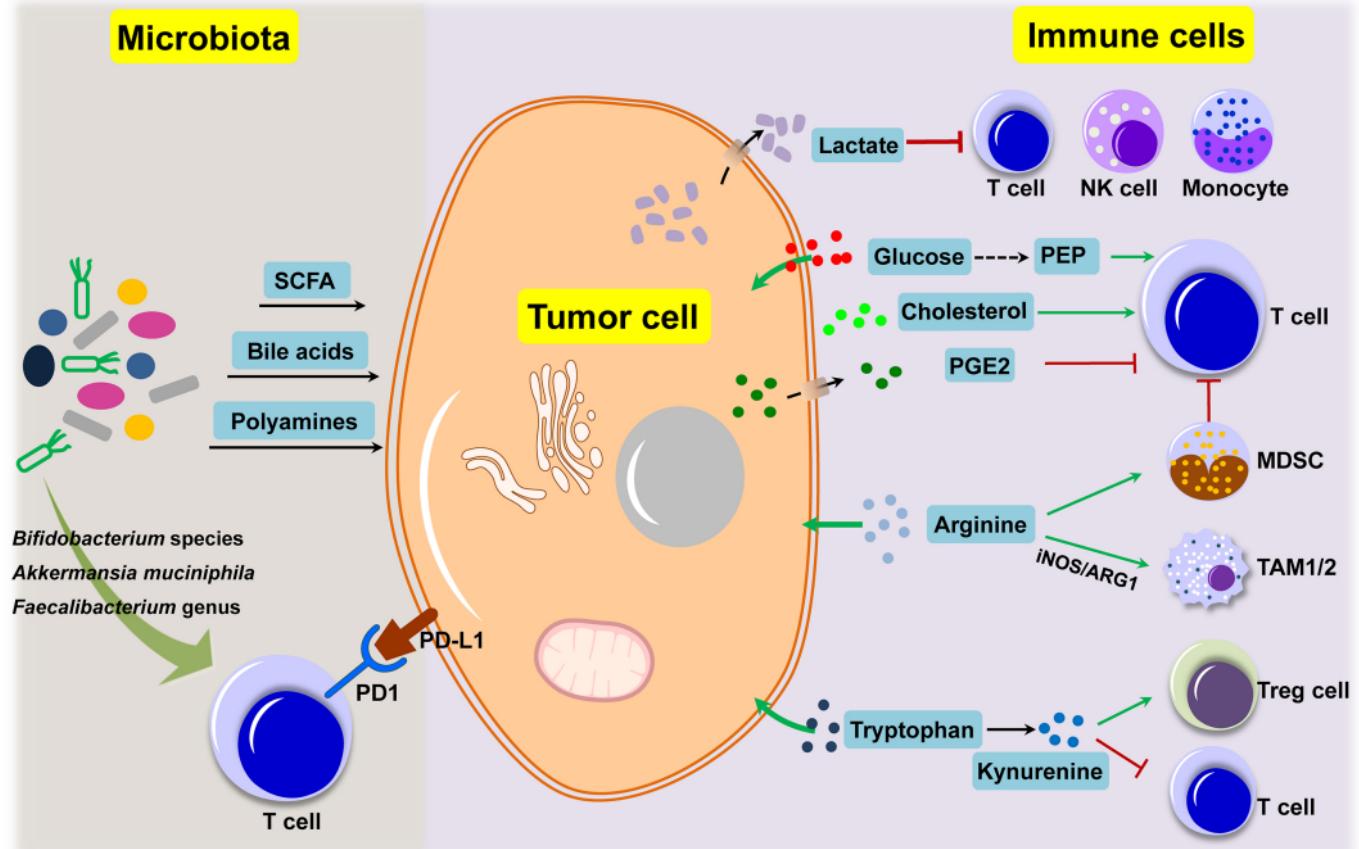


Figure 3