REVIEW ARTICLE

Metabolic Reprogramming and Molecular Rewiring in Cancer: Therapeutic Opportunities

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Abstract

BACKGROUND: A lot of contemporary cancer research has concentrated on genetic influence. However, cancer also involves biochemical changes, such as metabolic adaptation to support the aberrant cell proliferation.

CONTENT: The fast cell proliferation in cancer cells enforce a metabolic re-arrangement to promote their long-term survival. The increased glucose uptake and fermentation of glucose to lactate are common features of this altered metabolism known as "the Warburg effect". These metabolic pathways regulation enable cancer cells to produce adenosine triphosphate (ATP) in an efficient way. Epigenetic and metabolic changes also both affect molecular rewiring in cancer cells and promote cancer development and progression.

SUMMARY: Metabolic rewiring and epigenetic remodeling establishing a direct link between metabolism and nuclear transcription to promote the survival of tumor cells. A further understanding of how metabolic remodeling can result in epigenetic changes in tumors, affecting cancer cell differentiation, proliferation, and/or apoptosis, will lead to a new strategy for cancer therapy.

KEYWORDS: cancer metabolism, epigenetics, metabolic reprogramming, molecular rewiring

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Introduction

In order to survive and perform regular maintenance its critical cellular processes, all cells need a source of energy.(1) Therefore, cells must extract free energy from nutrients or sunlight. Additional energy and nutrients were required for growing and proliferating cells to synthesize building blocks and coordinate necessary reactions to build the macromolecules essential for constructing a new cell.(2-7) Normal cells rely on mitochondrial oxidative phosphorylation (OXPHOS) while most cancer cells altered the metabolic pathways into aerobic glycolysis. This give an initial hint that cancer cells alter the normal metabolic pathways to provide sustain the pool of energy and nutrients during their growth.(1)

From bacteria to humans, methylation and acetylation, as the chemical basis for epigenetics, are sensitive to cellular metabolic status. De-modification enzyme cofactors (α-ketoglutarate, Nicotinamide adenine dinucleotide (NAD^+)) and epigenetic enzyme inhibitors (*e.g.*, S-adenosylhomocysteine, 2-hydroxyglutarate) can easily affect methylation and acetylation. In microbes, methylation and acetylation initiating the protein evolution that roles in the metabolic environment. While mammalian extracellular environments are more tightly regulated, but the combined effect of nutrient abundance and metabolic enzyme expression can influence epigenetics gene regulation, including histone methylation, histone acetylation, and DNA methylation. The metabolic enzymes are sensitive to changes in intracellular metabolism and mutations, while also play a role in stem cell fate and cancer, such as isocitrate

dehydrogenase (IDH), succinate dehydrogenase (SDH), and fumarate hydratase (FH).(8) Furthermore, this concept provides understanding how alterations in metabolism and nutrition might contribute to disease.(9)

The hallmark characteristics of cancer cells are facilitated by its epigenetic plasticity (10,11), especially in adjusting the metabolism in order to sustain proliferation and keep the mitochondria alive, despite of changes in the availability of oxygen and nutrients (carbohydrates, lipids and amino acids) (3,12,13). The interaction between cellular metabolism and the epigenome contribute in how genetic invole in cancer process. A further integrative understanding of how cancer rewire the interaction between the molecular, metabolic and epigenetic will lead to a better strategy for cancer therapies.(14)

The Warburg Effect, Benefit for Cancer Cells

Cancer cells grow rapidly, so they need to rapidly increase the energy pool. Otto Warburg's in the 1920's discover a phenomenon named as “the Warburg effect”, where tumor cells took up more glucose and produced more lactate than normal cells. This give a hint that cancer cells reprogrammed their metabolism, refer as “aerobic glycolysis”.

Aerobic glycolysis is inefficient, because it needs more glucose to generate adenosine 5'-triphosphate (ATP), however it is not depend on the availability of oxygen (Figure 1), suggesting that cancer cells choose the inefficient ATP production to keep the sustainability of energy pool in a quicker way when the sources are scarce. Different with the normal cells proliferation where supply of glucose and other nutrients in circulating blood are always adequate. Warburg first proposed that cancer cells develop a mitochondrial deficiency, resulting in impaired aerobic respiration and a dependence on glycolytic metabolism.(15) However, subsequent research revealed that most cancer cells' mitochondrial function is unaffected.(16-18)

Aerobic glycolysis allows proliferating cells to have high ratios of ATP/adenosine 5′-diphosphate (ADP) and NADH/NAD^+ no matter how much they are stimulated to divide.(2,19) Any minor disruptions in the ATP/ADP ratio can impair growth, and cells will go through apoptosis or cell cycle arrest when ATP from glucose is deficient (19,20), then reactivate catabolic metabolism (21,22). Some signaling pathways exist to sense energy status, adenylate kinases, for example, buffer decreasing ATP output by converting two ADPs to one ATP and one adenosine 5'-monophosphate (AMP). While this helps to maintain a viable ATP/ADP ratio, but when the ATP keep declining, the accumulation of AMP activates AMP-activated protein kinase (AMPK).(23)

Some theories revealed that cells with a higher rate of ATP, but lower yield of ATP production may have a better survival rate in case of shared and limited energy resources. (24) The supply of glucose in tumor microenvironments is small, yet they compete with stromal cells and the immune compartment for nutrients.(23,24) A recent study reported that when ATP demand was greatly increased in the cellular environment, ATP-dependent membrane pumps were altered, aerobic glycolysis increased rapidly while oxidative phosphorylation remained constant.(25) This suggested the

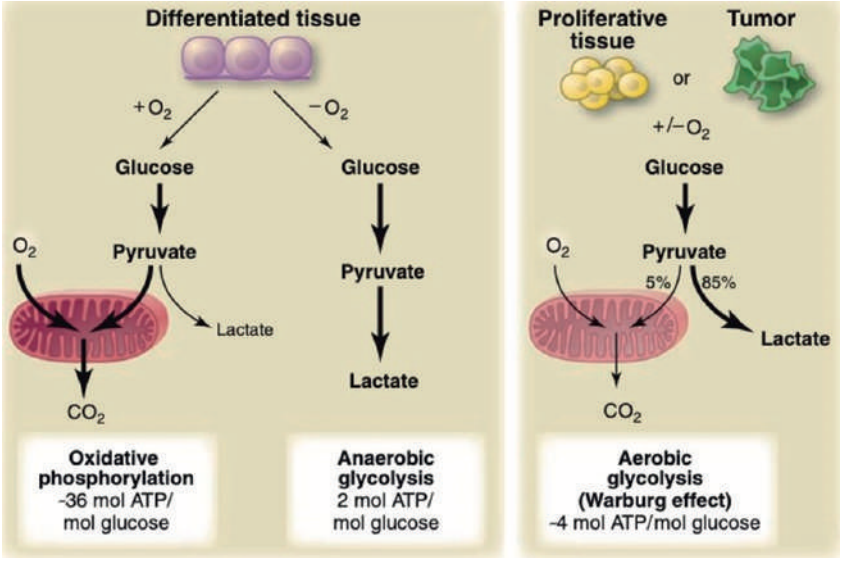

Figure 1. Schematic representation of the differences between oxidative phosphorylation, anaerobic glycolysis, and aerobic glycolysis (Warburg effect).(3) (Adapted with permission from American Association for the Advancement of Science).

Warburg effect has benefits to support the rapid production of ATP in challenging situations.

To provide cell building blocks in uncontrolled proliferation, the Warburg effect use an adapted mechanism increased glucose consumption as a carbon source for anabolic processes and generate nucleotides, lipids, and proteins from the excess carbon, for example the enzyme phosphoglycerate dehydrogenase (PHGDH) which diverse glycolytic flux into *de novo* serine biosynthesis.(25-29) Another argument said that instead of providing a rate-limiting need for ATP, proliferating cells need more NADPH and glucose, especially for lipid synthesis (Figure 2).(3,6)

Aerobic glycolysis produces high lactate which contributes to M2 tissue-associated macrophage (TAM) polarization.(30) It is also increase the supply of glucose to tumor-infiltrating lymphocytes (TIL) to perform their effector functions, as tumor and TILs are in competition for the availability of glucose, and the high rates of glycolysis limit the availability of glucose to TILs and hinder their function in eradicating the tumor cells.(23,24) Tumor cells can trick the immune system to support pro-tumor immunity and escape from immune check point.(31) The Warburg Effect alters glucose metabolism and confers direct signaling functions to promote tumorigenesis.(4,12,32-34) These signals affecting other cellular processes including the generation and modulation of reactive oxygen species (ROS) (35), and the mediation of chromatin state together with another possible signaling mechanisms.(27)

In mammals, nutrient intake is metabolized into glucose, glutamine, and lipids supply for cells differentiating and proliferating needs. Any imbalance of this fuels supply or the metabolism signal pathways can increase the risk of cancer.(36,37) Metabolism is involved in almost all a cell does, either directly or indirectly. In every multicellular organism, there is mounting evidence of cross-talk between signaling pathways and metabolic control. There is also much to learn about the regulation of proliferating cell metabolism. This critical aspect of biology would almost certainly have a major effect on our understanding of cell proliferation regulation and cancer.

Interaction of Pentose Phospate Pathway with Oncogenic Pathways

Recently, the discovery that malignant transformation and metabolic reprogramming may be inextricably linked has increased attention to aberrant cell proliferation. Despite

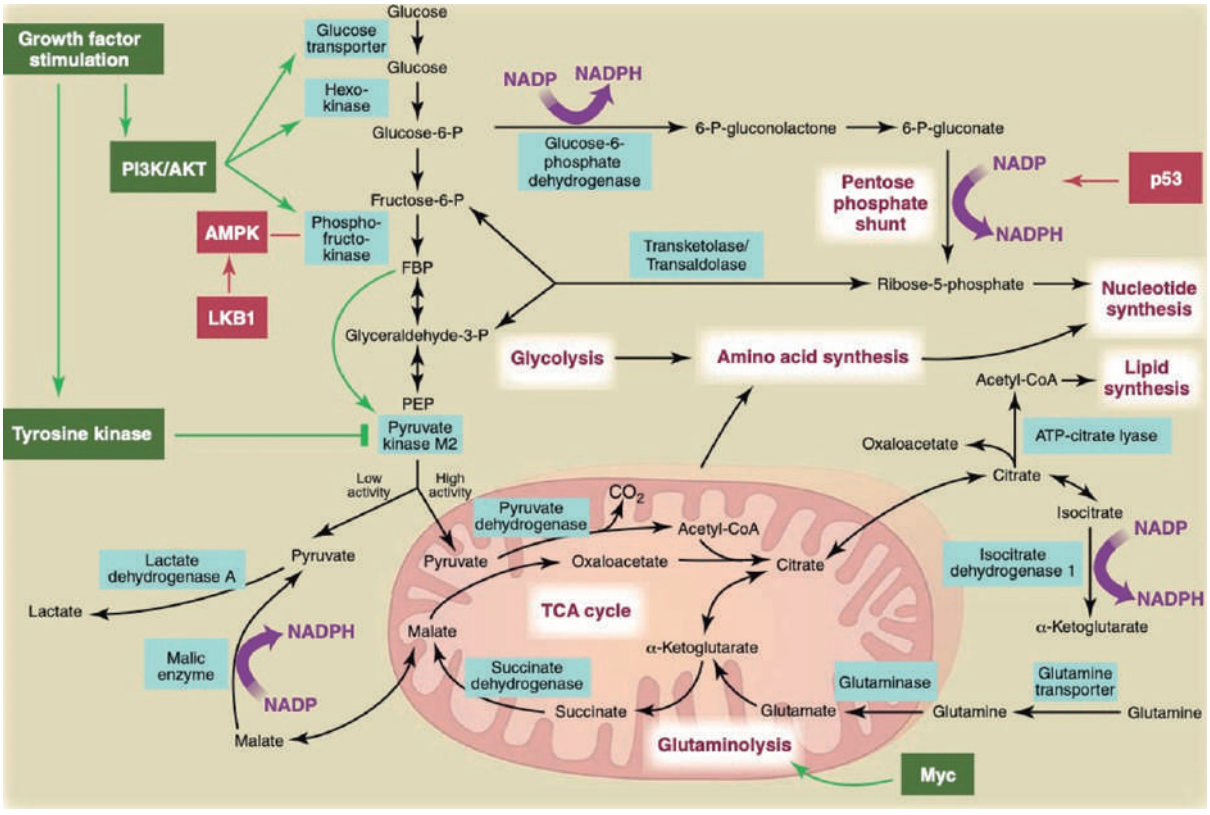

Figure 2. Metabolic pathways active in proliferating cells are directly controlled by signaling pathways involving known oncogenes and tumor suppressor genes.(3) (Adapted with permission from American Association for the Advancement of Science).

extensive research, cancer remains the world's second leading cause of death after cardiovascular diseases. While the last decade has seen a change in how cancer is treated, the application of glucose, glutamine, and lipids using small molecules, growth factors and their receptors, etc were not success. This is partially explained by the characteristic genomic instability of malignant cells, which results in an extraordinary capacity to adapt to and eventually resist the inactivation of 'cancer-specific' signaling pathways.(38,39)

Inhibition of the essential and irreplaceable processes needed by tumor cell proliferation represents a promising strategy for improving cancer therapy, for example tumor-specific metabolism. Despite its recognition nearly a century ago, the critical role of metabolic dysregulation in cancer pathogenesis has eluded the majority of cancer researchers for decades. Metabolic reprogramming was just widely accepted as a hallmark of cancer since the post-genome era.(11,40) However, in recent years, cancer metabolism and the interactions open a chance of new improved methodology in understanding cancer.(41) Metabolic changes observed are far from trivial, and can be quite specific depending on both the genetic lesion and the type of tumor tissue.(42) Most published research focused on the roles of glycolysis, glutaminolysis, and mitochondrial activity, while the role of pentose phosphate pathway (PPP) in malignant transformation has remained elusive for a long period of time.

After glycolysis and the tricarboxylic acid (Krebs) cycle, the PPP was found, and provoke the interest of Berlin-renowned Dahlem's Otto Warburg laboratory. In the 1930s, he discovered that the pyridine nucleotide diphosphopyridine nucleotide DPN (today known as NAD^+) functions as an electron transporter.(43,44) This proved the existence of a second coenzyme, which is triphosphopyridine nucleotide (TPN/$NADP^+$), is necessary for the oxidation of glucose 6-phosphate to 6-phosphogluconate by glucose 6-phosphate dehydrogenase (G6PDH).(43-45)

A cell's survival in an ever-changing environment is contingent upon a highly dynamic systems such as the robustness, connectivity, and functionality of its biological networks, in respond to changing endogenous and exogenous conditions through the interaction of a small number of discrete components.(46-51) The dynamic of metabolic network, involve a few hundred metabolites which are connected by biochemical interactions inside metabolic modules, delivering energy and biomolecules in response to substrate availability, enzyme activity, and cellular needs. As a result, metabolism is adapted to properly function to maintain the metabolic network's according to the environmental changes. These adaptations also entail the required components and decreased the unneeded components so the energy and resources can be conserved to assure the metabolic network homeostasis.(46,51-55)

Building blocks such as nucleotides, amino acids, and lipid precursors also need for cell growth. As a result, when cells undergo proliferation, they restructure their central carbon metabolism to accommodate the increased metabolic demands. This metabolic reorganization entails redirecting energy flow away from the mitochondria to fuel glycolysis and the PPP.(28,56-58) The PPP plays a critical, non-redundant role in the supply of the building blocks. Thus, redirecting energy flow to the non-oxidative branch of the PPP has the critical benefit of enabling the required nucleotide biosynthesis via the production of ribose 5-phosphate.(59) Additionally, by modulating NADPH production in the PPP, this metabolic restructuring maintains the cellular redox balance.(60)

Immunohistochemistry and gene and protein expression analyses are frequently used as surrogate methods for determining the role of specific factors in cancer pathogenesis. While these methods are undoubtedly useful and have aided in the identification of numerous molecules important for cancer biology, they are incapable of providing a valid and detailed characterization of metabolic pathways. Post-translational mechanisms appear to be the primary regulators of metabolic pathways.(61-63) The availability of cofactors ($NADP^+$ for oxidative PPP), substrates (non-oxidative PPP), and glycolytic enzyme affect PPP flow. As a result, data on mRNA and protein abundance is insufficient to pinpoint changes in PPP activity and their possible causative implications for cancer biology; hence, these values must be assessed in combination with flux and/or metabolite concentrations.

The gene that controls transcription, the tumor suppressor p53 is well-known for its involvement in genomic integrity, apoptosis, and cell cycle control.(64) It's also the most often mutated gene in human malignancies, implying that its loss is a key factor in control over metabolic pathways, and the therapeutic efficacy.(64,65) The p53 induced glycolysis regulatory phosphatase (TIGAR) gene has been found to suppress glycolysis by lowering fructose 2,6-bisphosphate, a powerful allosteric activator of Phosphofructokinase 1 (PFK1). As a result, glycolytic intermediates can be redirected to the PPP's oxidative or non-oxidative branches, and decreased cellular ROS levels as a result of NADPH action, which impact in increased cell survival and growth.(64)

The prognosis for certain types of cancer has improved in recent years (*e.g.*, breast and colon cancer). Otis W. Brawley, the American Cancer Society's chief medical officer, once stated, "One cancer cell is smarter than a hundred brilliant cancer scientists." Despite of so many causes of malignant transformation such as uncontrolled growth and therapeutic resistance, the that PPP activity was found to be predictive of cancer therapeutic efficacy.(66)

The Role of Lipid Metabolism in Cancer

Among the cell's component biomolecules, lipids are frequently overlooked in favor of proteins and nucleic acids. Lipids, are a complex group of biomolecules with a broad range of structure and function.(67) Sterols, monoglycerides, diacylglycerides, triglycerides, phospholipids, and glycolipids are all examples of hydrophobic molecules known as lipids. Phospholipids are the most abundant type of membrane lipids. They are further classified into phosphoglycerides, which contain two fatty acids (FA) esterified to a glycerol backbone; and sphingolipid, which contain one FA linked to an amino alcohol or sphingosine. Sphingolipids, are critical mediators of cellular signaling and survival.(68) Phosphoglycerides contain a variety of head groups, such as serine, ethanolamine, choline, glycerol, or inositol.

Glycolipids are membrane lipids that play a role in cell identification, inflammation, and immunity (69), which are made from sphingosine and FAs that have a sugar head group (glucose or galactose) on the exterior of the membrane bilayer.(70) The third major type of membrane lipid is cholesterol, which is composed of four linked hydrocarbon rings and regulates not only membrane fluidity but also the formation of microdomains (71), and acts a substrate for the synthesis of steroid hormones (72).

Apart from storing energy and forming membranes, FAs serve as precursors for the synthesis of signaling molecules known as lipid mediators. Arachidonic acid, a polyunsaturated FA (PUFA) derived from omega-6 FAs, via the cyclooxygenase pathway (COX), is the substrate for the synthesis of eicosanoids, such as prostaglandins and thromboxanes, and leukotrienes via the lipooxygenase pathway. Prostaglandins, including prostaglandin E2 (PGE2), contribute to tissue inflammation and contribute to the development of a tumorigenic environment.(73) Other PUFAs with signaling properties such as the omega-3 FAs eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have shown to reduce inflammatory processes and may help prevent breast and other cancers.(74) These multiple functions of FAs in membrane structure, energy metabolism, and signaling emphasize the FA levels regulation in cancer cells, including regulating the synthesis, modification, and uptake of FAs from the microenvironment, as well as their release from other lipid species. Numerous mechanisms regulate the abundance of FA in cancer cells.

Changes in lipid metabolism are one of the most common metabolic abnormalities in cancer. Increased lipid synthesis or uptake contributes to cancer cell proliferation and tumor formation.(75) As we discussed before, cancer cells rewire their energy machinery from OXPHOS to aerobic glycolysis, particularly in the hypoxic cores of solid tumors, and glycolysis occurs even in the presence of oxygen.(76) The high lactate produce by aerobic glycolysis increase the acidity of tumor microenvironment (TME), and inhibit dendritic and T cell activation, make it easier for tumor cells to invade.(77) Cancer cells' mitochondria still produce ATP, tricarboxylic acid cycle intermediates for lipid synthesis such as citrate, and also oxaloacetate for nucleotide synthesis which are required as precursors for macromolecule synthesis.(76) FAO is the primary source of acetyl-CoA for mitochondrial OXPHOS.(78)

Numerous studies have established that lipogenesis is required for tumor growth.(79) Indeed, multiple oncogenic signaling pathways intersect at the level of FA synthesis. The phosphoinositide 3-kinase (PI3K)/Akt signaling axis increases the production of FA-synthesis enzymes, and the phosphorylation and activation of ATP-citrate lyase (ACLY), to converts cytoplasmic citrate into acetyl-CoA. (80,81) By phosphorylating Acetyl-CoA carboxylase (ACC), the AMPK, which is regulated by the serine/threonine kinase 11 (STK11)/liver kinase B1 (LKB1) tumor suppressor pathway, inhibits FA synthesis.(82)

Historically, cholesterol was known to role in building cell membranes, but it is now recognized as a critical regulator of cellular function. Its presence in cell membranes has the ability to modulate transmembrane receptor activation (83), and has a wide range of biologically active metabolites, including oxysterols and isoprenoids (84). Cholesterol was needed to synthesize hormones. That is why, the demand for cholesterol is greater in hormone-dependent cancers than in other tumor types (85), and inhibiting cholesterol synthesis can be detrimental to cancer cells (86). Statin, a class of compounds inhibiting β-Hydroxy β-methylglutaryl-CoA (HMG-CoA) reductase has been tested for treating cancer (87-89), and their lipid biosynthesis inhibition effect on cancer cell survival and tumor growth, although several

other studies failed to establish a clear benefit of statins in cancer prevention or adjuvant therapy.(90-92)

Some compounds targeting fatty acid synthase (FASN) gene also developed and tested in different cancer models.(93) Additionally, inhibiting ACC1 and ACC2 with the allosteric inhibitor ND-646 inhibited tumor growth in both the Kras/p53$^{-/-}$ and Kras/Stk11$^{-/-}$ mouse models of non-small-cell lung cancer when used alone or in combination with carboplatin.(94) Inhibiting FASN was shown to prevent the formation of metastases observed following the cessation of anti-angiogenic therapy.(95) However, the exact mechanism is remains unresolved. Sterol regulatory element-binding protein 1 (SREBP1) demonstrated to induce a transcriptional pathway characteristic of epithelial to mesenchymal transition (EMT) in breast cancer by recruiting a SNAIL/HDAC1/2 repressor complex to the E-cadherin promoter. SREBP1 performs this function, however, by directly binding to the E-cadherin promoter rather than by regulating FA synthesis.(96)

While reactivation of FASN is now a well-established component of the metabolic reprogramming that occurs during transformation, it is becoming increasingly clear that FA oxidation (FAO) is also required for cancer cell survival in a variety of cancers. Numerous malignancies have been associated with an overexpression of FAO enzymes (97), and inhibiting FAO inhibits tumor growth. In an orthotopic patient-derived xenograft (PDX) triple-negative breast cancer (TNBC) model and an orthotopic glioblastoma model, inhibiting carnitine palmitoyltransferase 1 (CPT1), the rate-limiting enzyme in FAO, has been demonstrated to reduce tumor development and prolong life.(98-100)

The presence of large quantities of the enzyme monoacylglycerol lipase (MAGL), which releases free FAs from monoacylglycerol during lipolysis, in aggressive cancer cell lines, *i.e.*, those with a larger capability for migration and tumor development, offered evidence for a more direct involvement for FAs in metastasis development. (100) MAGL expression induced a distinct lipid signature and indicates the aggressive disease. In the absence of MAGL, a high-fat diet (HFD) rescued tumor growth (100), means that fat diet also contribute in promoting disease progression. Similarly, the increased metastasis formation observed in phosphatase and TENsin homolog (PTEN)$^{-/-}$ prostate cancer was attributed to continued expression of sterol O-acyltransferase 1 (SOAT1).(101) Thus, regarding the importance of lipid for cell maintenance, it is important to keep the balance of PUFAs for the production of lipid mediators that regulate immune evasion and their potential detrimental effect on sensitization to lipid peroxidation and ferroptosis. Except for the FASN inhibitor TVB-2640, which is now being studied in phase II clinical trials as a single agent in non-small cell lung cancer with KRAS mutations (NCT03808558) or in combination with paclitaxel and trastuzumab in TNBC (NCT03808558), no drugs targeting FA metabolism have shown a promising outcome till recently (NCT03179904). The ACC1/2 inhibitor ND-630 is currently undergoing phase I testing for the treatment of non-alcoholic steatohepatitis (NCT02876796).(79)

The PI3K-AKT Network at the Interface of Oncogenic Signaling and Cancer Metabolism

The PI3K–AKT pathway is the most often activated pathway in human malignancies.(102) It enhance the metabolic enzyme and nutrient transporters activity thus alter the cellular metabolism, allowing developing cells to satisfy their anabolic requirements. Src homology 2 (SH2) domains inside regulatory subunits connect with phosphotyrosine residues on active receptors, for example receptor tyrosine kinases (RTKs) or cytokine receptor or adaptor proteins to activate class Ia PI3K, whereas G protein-coupled receptors (GPCRs) activate class Ib PI3K. As the 'druggable' character of metabolic enzymes attests, understanding how the PI3K–AKT pathway regulates metabolic networks in normal cells and how this regulation is change in cancer cells may uncover metabolic vulnerabilities and so inspire novel treatment tactics.(103)

While both PI3K and AKT have a large number of downstream effectors that affect the function of normal and cancer cells, we will focus on those that affect cellular metabolism. AKT signaling can affect metabolism. It make impact directly through phosphorylation-mediated control of metabolic enzymes, allows for quick changes in the activity of metabolic pathways and the directionality of metabolic flow. This direct impact also activates a few critical downstream effectors involved in cellular metabolic reprogramming, including mammalian target of rapamycin complex 1 (mTORC1), glycogen synthase kinase 3 (GSK3), and transcription factors from the forkhead box O (FOXO) family. While indirectly, Akt signaling control the different transcription factors. Gene expression control systems are usually used to make longer-term changes in cellular metabolism.(104)

The FOXO family of transcription factors (FOXO1, FOXO3A, and FOXO4), sequestered from the nucleus upon phosphorylation, to prevent their target genes from being

expressed.(105,106) AKT-mediated FOXO inhibition has been implicated in various facets of cancer development and progression, which includes multiple growth, proliferation, and survival inhibitors, as well as particular metabolic enzymes.(107)

PI3K–AKT pathway can control several aspects on metabolic programme, including to promote aerobic glycolysis (108,109), enhancing glucose uptake and the rate of glycolysis (108-113), thus render cancer cells which depend on glucose for survival (109,113). This setting contribute to cancer cell macromolacules synthesis (1), and these biosynthetic processes are also further regulated downstream of AKT. While mitochondrial metabolism via the tricarboxylic acid (TCA) cycle has been identified as a process capable of meeting the energetic and biosynthetic demands of proliferating cancer cells (114,115), the PI3K–AKT pathway's defined functions in direct control of the TCA cycle remain unknown. It is possible that under aerobic glycolysis conditions, the PI3K–AKT pathway promotes anaplerotic metabolism to maintain TCA cycle flux, for example, by activating MYC (Figure 3).(116,117)

Abnormal activation of lipid biosynthesis is a characteristic of many cancer cells.(79) Apart from utilizing FAs derived from the bloodstream, cancer cells initiate de novo lipid biosynthesis in order to facilitate the formation of cellular membranes and support their increased growth and proliferation.(118) The PI3K–AKT pathway stimulates de novo lipid synthesis via both post-translational and transcriptional pathways. Sterols and FAs are made from cytosolic acetyl-CoA, by ACLY or acetyl-CoA synthetase pathway utilizing citrate from TCA cycle intermediate.

Nucleotides, which are built from purines and pyrimidines, are necessary building blocks for the synthesis of nucleic acids (RNA and DNA), as well as for a variety of other cellular functions.(119) Cancer cells stimulate robust de novo synthesis of nucleotides for cell growth

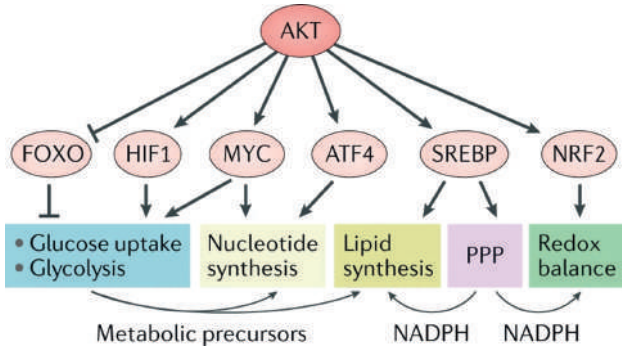

Figure 3. Transcriptional control of metabolic processes downstream of AKT signalling.(117) (Adapted with permission from Springer Nature).

and proliferation (120,121), require coordinated input from multiple metabolic pathways, including PPP, serine, and glycine synthesis, glutamine uptake for ribose sugar need, one carbon metabolism, and aspartate synthesis from oxaloacetate synthesized in TCA cycle, completing with essential atoms to form the pyrimidine and purine bases. As a result, AKT signaling appears to regulate nucleotide synthesis via multiple parallel mechanisms involving these metabolic inputs.

mTORC1 is as a downstream effector of PI3K–AKT signaling and has emerged as a significant regulator of *de novo* nucleotide synthesis. Growth factor signaling to mTORC1 stimulates pyrimidine synthesis acutely by phosphorylating and activating the pathway's first and rate-limiting enzyme, carbamoyl-phosphate synthetase 2, aspartate transcarbamylase, and dihydroorotase (CAD), which catalyze the first three steps of pyrimidine biosynthesis. (119,122) Inhibitors of the enzyme inosine monophosphate dehydrogenase (IMPDH), such as mizoribine, a commonly used immunosuppressant in Asia, have been demonstrated to be very sensitive to cancer cells produced *in vitro* and tumor models developed *in vivo* with uncontrolled mTORC1 or MYC activation.(123,124) IMPDH is required for the synthesis of guanylates, which are abundant in pre-rRNA (37%). Thus, when ribosome biogenesis is active in cells, rRNA synthesis depletes guanylates more quickly, depriving cells of nucleotides for DNA synthesis and resulting in replication stress and death in response to IMPDH inhibitors.(123) In conditions with enhanced ribosome biogenesis, such as those with active mTORC1 or MYC, such medicines may be potent and selective anticancer agents despite their immunosuppressive qualities. Specifically, chemotherapeutic drugs that limit nucleotide synthesis, such as methotrexate and 6-mercatopurine, have been demonstrated to impair mTORC1 signaling via a purine, but not pyrimidine, nucleotide depletion mechanism. (125-127)

Consistent with the importance of PI3K signaling in the cellular response to ROS, an increase in ROS levels can activate the pathway via a variety of mechanisms. By oxidizing cysteine residues on proteins, including the catalytic cysteine of protein and lipid phosphatases, H_2O_2 can affect cell signaling events. Among these ROS-sensitive phosphatases are inhibitors of PI3K signaling, including protein tyrosine phosphatase 1B, protein phosphatase 2A, PTEN (128-130), and the inhibitory oxidation of which can activate AKT in response to a rise in H_2O_2 (129,130). Together these serve as part of an adaptive oxidative stress response pathway.

Specific inhibitors of both PI3K and AKT have been developed as cancer therapies, but the majority of trials demonstrating limited therapeutic benefit when used alone.(131) And because of PI3K–AKT critical role in insulin-responsive glucose uptake into tissues such as skeletal muscle, pan-PI3K inhibitors invariably result in hyperglycemia, or hyperinsulinaemia, with a risk to reactivate PI3K signaling in tumors. In mouse cancer models, dietary interventions such as the ketogenic diet have been shown to alleviate this hyperglycemia and hyperinsulinaemia and improve response to these inhibitors.(132) Additionally, resistance to PI3K inhibitors may develop as a result of redundant regulation of important downstream effectors such as mTORC1.(133) Interestingly, when combine with an estrogen receptor antagonist, the use of a p110-selective PI3K inhibitor (BYL719, trade name Piqray) in 40% patient stratification for oncogenic PIK3CA mutations of ER^+, $HER2^-$ breast cancers, resulted in improved clinical responses.(134)

In the end, while we've focused on cancer cells' intrinsic control of metabolism, apparently the physiological properties of the tumor's origin tissue, the stromal cell milieu, the host's nutritional and metabolic condition, and the diverse metabolic habitats of distant metastases have a differential impact on cancer cell metabolism and metabolic dependencies.(127)

The Importance of Serine Metabolism in Cancer

Metabolic homeostasis is maintained in nondividing cells by fueling housekeeping processes with ATP, therefore nonproliferating cells also have responsibility to generate energy from nutrient. Proliferating cells, on the other hand, must accumulate the biomass required to build a new cell, including nucleotides for genome replication and ribosomal RNA, lipids for membranes, amino acids for proteins, and other biological building components. Not only ATP is required for the biosynthesis of these macromolecules, but also carbon and nitrogen precursors (1), as well as electron acceptors to maintain redox balance (135).

The folate and methionine cycles integrate nutritional status from amino acids, glucose, and vitamins to generate a variety of outputs, including lipid, nucleotide, protein biosynthesis, redox status maintenance, and substrates for methylation reactions. This pathway apparently is more complicated than just a 'housekeeping' process. Some study show the link between cellular epigenetic status and oncogenesis (Figure 4). Since there are abundance of clinically available agents that inhibit one-carbon metabolism, these new findings may pave the way for the translation of these findings into precision cancer medicine. (136) Some modern cancer therapy strategy is based on the concept that antagonists of folate metabolism and its downstream effectors, such as nucleotide metabolism, and can limit the growth of cancerous blood cells.(137-140)

Cancer cells metabolism alteration showed an Increasing in serine production, and serine is a key component of many compounds' production such as glycine and cysteine.(141,142) Glycine is a precursor of porphyrins, as well as a component of purine nucleotide bases and glutathione (GSH). Serine is also a headgroup, or precursor to a headgroup, for phospholipids and is essential for the production of sphingolipids via sphingosine. Additionally, serine contributes carbon to the one-carbon pool involved in the metabolism of folate. Serine hydroxymethyltransferase (SHMT) catalyzes the conversion of serine to glycine, which donates a one-carbon unit to tetrahydrofolate to form 5,10-methylenetetrahydrofolate (CH2-THF). CH2-THF is a precursor for various folate species involved in purine synthesis and is employed in the production of thymidine. Folates are needed to regenerate methionine from homocysteine, allowing for the production of S-adenosylmethionine (SAM), the methyl donor for DNA and histone methylation processes that regulate gene expression epigenetic control. As a result, an increase in serine availability might help cancer cells that are growing.

Numerous tumors upregulate PHGDH expression and SSP flux, and PHGDH activity is required for tumor growth *in vivo* under certain conditions. However, additional research is necessary to determine the time point at which tumors are susceptible to PHGDH inhibition. Any attempts to treat patients with small molecules that inhibit PHGDH must account for the possibility of neurological symptoms if the inhibitor crosses the blood–brain barrier. Anyhow, there is no specific way to determine patient's respond to PHDGH inhibitor, since not every cancer cells dependent to SSP flux. The control of pyruvate kinase (PK) is correlated with glucose-derived serine and nucleotide synthesis, which might be important in tumor formation. The penultimate phase of glycolysis is catalyzed by PK, which links ATP production to pyruvate production from phosphoenolpyruvate (PEP). Despite of various isoforms of PK, the M2 isoform (PKM2) is more commonly seen in cancer, and its activity can be influenced by a range of signaling molecules and metabolite levels.(143) Serine activates PKM2 allosterically, with an AC_{50} of 1.3 mM.(144-146) Serine synthesis pathway (SSP)

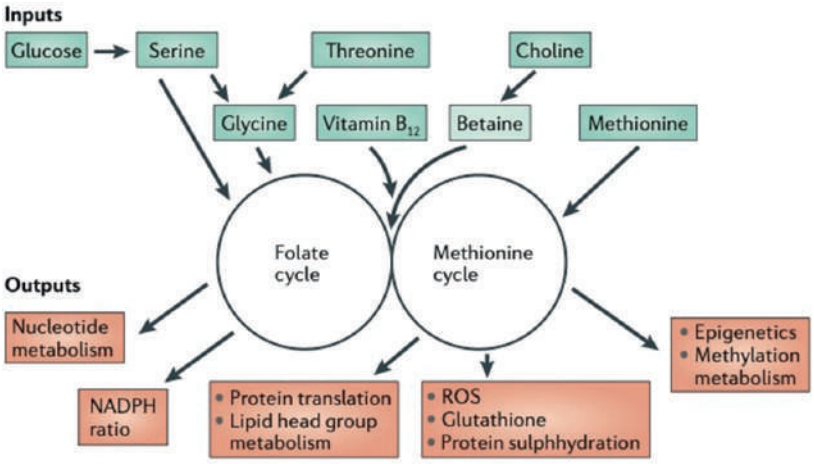

Figure 4. One-carbon metabolism as an integrator of nutrient status.(136) (Adapted with permission from McMillan Publishers).

activity is also influenced by PK activity, as cells with a high PK activity synthesize a smaller fraction of serine from glucose than cells with a low PK activity.(146-149) PEP and citrate levels increase in the absence of PKM2, whereas pyruvate and lactate levels decrease. Growing cells in a serine- and glycine-free media simulates these changes, and this approach allows cells to modify PK activity in response to cellular serine needs.(146)

Supporting data presents the critical role of extracellular serine and SSP flux in cancer continues to grow. In some cases, low level of serine can inhibit cancer cells proliferaton, and lead to nucleotide precursors depletion since it is lack of one-carbon units.(150,151) However, even when serine is available, cells with PHGDH amplification require SSP flux.(152-154)

Recent work in cancer metabolomics has revealed that individual metabolic fluxes were correlated with cell proliferation, and it was discovered that glycine uptake was most strongly associated with cancer cell proliferation especially in rapidly dividing cells.(155) Additionally, glycine decarboxylase (GLDC) activity has been linked to the causal role of tumorigenesis. A subset of tumor-promoting cells overexpressed GLDC, and the ectopic GLDC expression was enough to cause tumor development in NIH3T3 cell xenografts.(156) In NIH3T3 cells, ectopic expression of two additional enzymes involved in serine and glycine catabolism, phosphoserine aminotransferase (PSAT) and SHMT, therefore might trigger tumor growth *in vivo*.

Notably, tumorigenesis was dependent on GLDC's enhanced enzymatic activity. Additionally, another study reported that increased availability of glycine or sarcosine may increase prostate cancer cells' invasiveness.(157) Taken together, these findings suggest that glycine uptake and catabolism contribute to tumorigenesis and malignancy. One of the earliest modern chemotherapies developed as a result of the discovery that vitamins B can stimulate red blood cell production and can treat anemia patients. While Sydney Farber found that B vitamin intermediates may oppose cell growth, while folic acid enhanced the growth of acute lymphoblastic leukaemia (ALL) cells. (137) In the end they found that aminopterin can induce remissions in children with ALL.(138,158) To this day, chemical derivatives of the initial folate antagonists, such as methotrexate and pemetrexed, constitute a significant class of cancer chemotherapy agents, works by inhibit dihydrofolate reductase and tetrahydrofolate reductase activity in humans, resulting in the disruption of one-carbon metabolism, and are used as first-line therapy for a variety of cancers, including ALL, breast cancer, bladder cancer, and lymphomas.(139,159-165). However, these agents' disruption of one-carbon metabolism is not effective against all cancer types. Recent findings may revealed on why this variation exists and may help identify patients who will benefit the most from these drugs.

Protein Phosporylation and Cancer

The plasticity and dynamics of chromatin are critical during cell division and interphase for an organism's development and maintenance of health. One of the most critical post-translational modification (PTMs) is protein phosphorylation.(166,167) Numerous phosphorylation of proteins sites in several chromatin regulators have been shown to reversibly alter the structure and function of chromatin, that occurs via protein kinases and involves the addition of a phosphate group (PO4) to the polar group R of

various amino acids.(168) This result in polarity conversion from hydrophobic to hydrophilic in response to other molecule, thereby assembling and disassembling protein complexes.(169) It is a critical regulator of the majority of many cellular processes, including enzyme activation and deactivation mediated by specific kinases and phosphatases.(170)

There are about 568 protein kinases and 156 protein phosphatases in the human genome. These enzymes are involved in the control of biological processes including as proliferation, differentiation, and death via regulating phosphorylation events. For example, phosphorylation activates the p53 protein, which then stimulates gene transcription to inhibit the cell cycle, activate DNA repair, and, in some cases, induce apoptosis.(171) Unbalanced phosphorylation/dephosphorylation of the p53 protein can result in the protein's chronic inactivation, which can transform the cell into a cancer cell.

Protein kinases are members of the large family of kinases and are responsible for the phosphorylation mechanism. The 518 human protein kinases are divided into groups based on which amino acid residues they phosphorylate.(169) The kinases can be activated or deactivated in a variety of methods, including cis-phosphorylation/autophosphorylation of the kinase, interacting with activator or inhibitor proteins, or assessing their location in the cell in relation to their substrate (172), and later initiates a series of processes that results in the phosphorylation of various amino acids. The majority of kinases operate on both serine and threonine (serine/threonine kinases; STKs), some only operate on tyrosine (tyrosine kinases; TKs), or all three (dual-specificity kinases; DSKs).(173) At least 125 of the human protein kinases are STKs (174), and the remainder can phosphorylate STKs and TKs (175).

Phosphatases function in the opposite way that kinases do. Phosphoric acid monoesters are hydrolyzed to produce a phosphate group and a molecule containing a free hydroxyl group.(176,177) In comparison to protein kinases, protein phosphatases are considered passive housekeeping enzymes; their distinct structure makes them more difficult to identify and less important than protein kinases.(178) PPP family, metallo-dependent protein phosphatase (PPM) family, and protein-tyrosine phosphatase (PTP) family (179) are the three families of around 226 protein phosphatases that are currently known.(180)

Protein phosphorylation is a critical initial step in the coordination of cellular and organic functions such as metabolism regulation, proliferation, apoptosis, subcellular trafficking, and inflammation, among others. In phosphorylation, a highly prevalent PTM involved in the regulation of numerous biological processes and kinase overexpression. Aberrant activation or dysregulation of kinase signaling pathways can be caused by mutations or defects in regulatory mechanisms.(181) This also the basis of oncogenesis for multiple tumors.(11,182,183) Cancer can arise not from genetic mutations, but also from epigenetic changes (184-186) that mainly disrupt the regulation of signal transduction pathways and alter the normal cellular mechanisms.(40) Kinase targets include a number of important regulatory proteins that control gene expression. The addition of a phosphate group to a protein by a kinase can change its activity, and this effect is often utilized as a switch on or off mechanism.(187,188)

Protein kinases-regulated signaling pathways play a role in the initiation and progression of almost all types of cancer. As a result, studies of the signaling pathways mediated by kinases and the possible target therapy to inhibit them could have significant clinical-therapeutic utility, particularly given that many of these proteins act as oncogenes.(11,189,190) Considerable progress has been made in the identification of inhibitors of activated tyrosine kinases in cancer, with 17 already being used to treat a variety of cancers and more than 390 molecules being tested.(191)

Imatinib (Glivec®) is a well-established inhibitor that inhibits the BCR-Abl tyrosine kinase in patients with chronic myeloid leukemia (CML) (192,193), and targets against PI3K in solid tumors (194,195), STK BRAF to treat melanoma (196-198), the receptor TK epidermal growth factor receptor (EGFR) for lung cancer (199,200), and STK mTOR for the treatment of renal tumors (201). Gefitinib/erlotinib (Tarceva®) acts against EGFR in lung tumors (202) with a 71.2% success rate (199), whereas crizotinib (Xalkori®) acts against EML4-ALK in the same tumor (203). In melanoma, vemurafenib (Zelboraf®) is directed against BRAF V600E (204) mutations and has a 48 percent success rate during treatment (197).

Another example is human epidermal growth factor receptor 2 (HER2), a protein TK that promotes cancer cell proliferation and the formation of blood vessels, thereby increasing breast cancer's invasiveness. The use of trastuzumab (Herceptin®), a monoclonal antibody directed against this protein, is currently improving the prognosis of this cancer.(205) Sorafenib (Nexavar®) is another kinase inhibitor that inhibits Raf kinase activity in renal and liver tumors.(206) Sunitinib (Sutent®) is a receptor TK inhibitor that targets platelet-derived growth factor (PDGF)

as well as vascular endothelial growth factor receptors (VEGFRs).(207) When both of these targets are inhibited at the same time, tumor vascularization is reduced and cancer cells undergo death. It's been recommended as a therapy for gastrointestinal stromal tumors (GISTs) and renal cell carcinoma.(208,209)

The success of kinase inhibitor therapies depends on several factors, including the clinically relevant kinase, the structure of the signaling network, and the mechanisms of innate or acquired resistance. To begin, both patients and therapeutic approaches must be appropriately chosen.(189) For example, this therapy is only effective in CML patients who are BCR-ABL positive, because BCR and ABL (Philadelphia chromosome genes) are the major targets, fused together via an activated protein TK. Similarly, Herceptin showed a 34 percent response rate in individuals whose tumors had amplified HER2, compared to 7% in those whose tumors did not have amplified HER2.(210)

Another critical aspect is phosphoproteomics which plays a role in understanding the molecular mechanisms underlying tumor genesis and growth.(11,181,182) As some drug kinase inhibitors are already on the market (192,203-207), their effectiveness is frequently diminished due to the development of complex drug resistance mechanisms.(211) However, significant progress has been made in proteomics techniques, and can be applied for determining the locations and behavior of phosphoproteins and phosphosites in tumor biology. Developing biomarkers to aid in the selection of the most appropriate therapy for individual patients continues to be a significant challenge.(212,213).

Mitochondrial Metabolism as A Target for Cancer Therapy

Mitochondrial metabolism is active and essential for tumor development, both in human and mice. It stimulates tumor anabolism by providing necessary metabolites for macromolecule synthesis and producing oncometabolites that aid in the maintenance of the cancer phenotype.(214) Tumor cells adapt their metabolic phenotypes to the unique requirements of the tumor microenvironment (215,216), as one of their survival strategies for accumulating the biomass required for continuous proliferation even in the presence of limited oxygen and metabolites.(217-219) Additionally, numerous clinical trials are being conducted to determine the efficacy of inhibiting mitochondrial metabolism as a novel cancer therapeutic strategy.

Tumor cells undergo metabolic reprogramming in response to driver mutations, by increasing or decreasing the metabolic flux relative to their premalignant tissue of origin.(114) As a result, these cells engage vigorously in glycolysis and its branching pathways (Figure 5), as well as TCA cycle metabolism, to generate ATP, NADPH, and the building blocks required for macromolecule synthesis (nucleotides, lipids, and amino acids), all of which are essential for cell proliferation.(220)

The enhanced glycolysis and TCA cycle flux found in cancer cells is due to the activation of important oncogenic drivers such as Myc and Kras, as well as dysregulation of signaling networks such as the PI3K pathway. The increased glycolytic rate allows for the generation of metabolic intermediates that can be diverted to a variety of biosynthetic pathways required for cell proliferation, such as the PPP for ribose and cytosolic NADPH production, respectively, to maintain nucleotide synthesis and antioxidant activity, and one-carbon metabolism for mitochondrial NADPH production.(114,216) The TCA cycle generates metabolites that are used in the synthesis of nucleotides, lipids, amino acids, and heme.(221) For example, a glycolytic metabolic signature is present in the early stages of colorectal cancer (CRC), involves downregulation of the mitochondrial pyruvate carrier (MPC), and connects glycolysis and glucose oxidation via mitochondrial pyruvate import. (222)

Glutamine is a critical nutrient in cancer cells because it regulates energy production, redox homeostasis, and signaling. Despite glutamine's essential role in mitochondrial metabolism, the mitochondrial glutamine transporter has remained unknown for a long period of time. By transporting glutamine into mitochondria, we demonstrate that the SLC1A5 variant is critical for cancer metabolic reprogramming. Overexpression of the SLC1A5 variant promotes glutamine-induced ATP and glutathione synthesis in pancreatic cancer cells and confers resistance to gemcitabine. SLC1A5 variant suppression and overexpression both affect cancer cell and tumor growth, implying an oncogenic role. SLC1A5 variant is a glutamine transporter involved in cancer metabolic reprogramming. (223) Metabolic reprogramming appears to be a dynamic process that continues throughout carcinogenesis, with metabolic flexibility suiting the tumor's demands at each step, from the initiation of tumor until metastasis.(224)

Solid tumors can be nutrient-deficient, due to its poor vascularization to supply glucose and oxygen.(225) The cores of these tumors continue to respire as the mitochondrial electron transport chain (ETC) can function optimally at

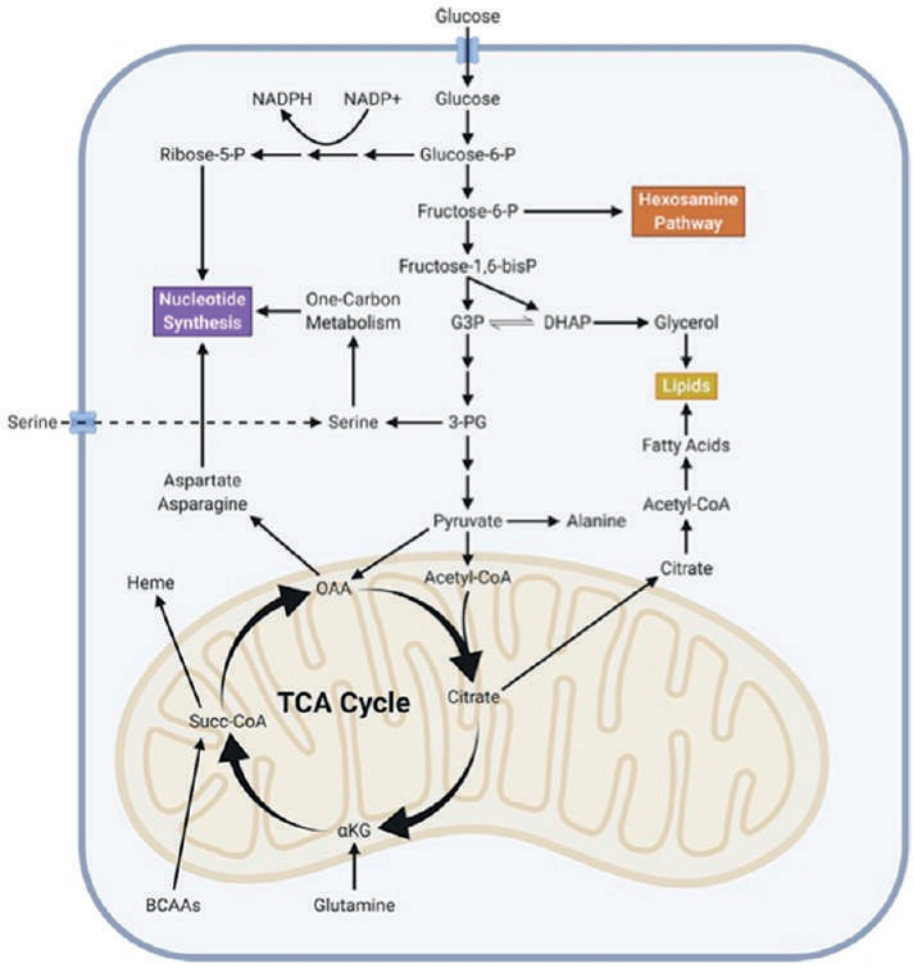

Figure 5. Metabolism supports macromolecule synthesis for growth.(214) (Adapted with permission from Elsevier).

oxygen concentrations as low as 0.5 percent.(226,227) As a result, tumor cores with poor vascularization have limited glucose availability but sufficient oxygen to continue generating mitochondrial ATP for survival. Additionally, as discussed previously, decreasing ETC function inhibits the oxidative TCA cycle, thereby decreasing macromolecule synthesis necessary for tumor growth. To date, the biguanide metformin has been tested in multiple clinical trials as an anticancer agent in combination with standard of care therapies as a putative mitochondrial ETC complex I inhibiton.(228)

According to some studies, patients who began taking metformin for blood sugar control after developing cancer had a higher chance of survival.(229) Additionally, numerous laboratory studies have demonstrated that metformin has anticancer properties.(113,230-233) A multi-center phase III clinical trial (*Clinical Trials.gov* identifier: NCT01101438) at the University of Toronto will report its findings next year to determine the feasibility of metformin (1,750 mg/day) as a breast cancer therapeutic strategy.(234) The proposed mechanisms by which metformin may exert its antitumor effects is that metformin decreases circulating insulin levels, a known tumor-stimulating hormone.(235) Insulin and insulin-like growth factors (IGFs) can activate the PI3K signaling pathway, which is pro-tumorigenic.(236) This, however, is true only for tumors that express insulin and/or the insulin growth factor receptor.

By sustaining dihydroorotate dehydrogenase (DHODH) activity, the mitochondrial ETC is intrinsically linked to pyrimidine nucleotide synthesis.(237) DHODH catalyzes the ubiquinone-mediated oxidation of dihydroorotate to orotate, the fourth enzymatic step in *de novo* pyrimidine biosynthesis on the outer surface of the outer mitochondrial membrane.(238,239) A recent study reported that the availability of ubiquinone to accept electrons from dihydroorotate, which is compromised only when mitochondrial complex III is inhibited, is a critical factor in maintaining *de novo* pyrimidine synthesis.(240) DHODH activity is reliant on mitochondrial complex III function, but has no bearing on the ETC's role in oxidative phosphorylation or the TCA cycle. Inhibition of DHODH has been demonstrated to be effective in a number of

preclinical cancer animal models, including extremely aggressive small cell lung cancer (SCLC), acute myeloid leukemia (AML), TNBC, and Kras-driven malignancies. (241-247)

Due to the TCA cycle's important role in the production of intermediate metabolites required for growth, drugs inhibiting the TCA cycle should be effective. CPI-613 is a new lipoate analog that block α-ketoglutarate dehydrogenase (α-KGDH) and pyruvate dehydrogenase (PDH), the major TCA cycle enzyme.(248) Although the mechanism by which CPI-613 exerts its anti-cancer activity is unknown, it demonstrated a significant therapeutic index in promising phase I and II results in pancreatic cancer and acute myeloid leukemia (NCT01835041).(249,250) CPI-613 is now on phase III clinical trials (NCT03504410 and NCT03504423) in patients with relapsed/refractory AML or metastatic pancreatic adenocarcinoma.

Glutamine is the primary carbon source for replenishing TCA cycle intermediates and sustaining their use in macromolecule biosynthesis.(251) Mitochondrial glutaminase (GLS1) converts glutamine to glutamate, and inhibit of GLS1 in mouse with lymphoma, and liver cancer driven by MYC shows good results.(252-255) Glutamate carbon incorporation into the TCA cycle (Figure 6) is observed in human renal cell carcinomas. (256) The combination of mTOR inhibitor Everolimus or the multi-tyrosine kinase inhibitor Cabozantinib with CB-839(Telaglenastat) is now in phase II clinical trials (NCT03163667 and NCT03428217) to treat patients with advanced or metastatic kidney cancer.

Inhibitors of mitochondrial metabolism may also be used in conjunction with therapies that impair glucose metabolism, such as combination with a PI3K inhibitors. Additionally, certain cancer cells, such as early-stage lung adenocarcinoma, express excessive amounts of the sodium-dependent glucose transporter 2 (SGLT2). In preclinical autochthonous mice models and patient-derived xenografts, blocking SGLT2 using USA Food and Drug Administration (FDA)-approved inhibitors, the gliflozins, decreased lung cancer growth and extended lifespan.(257)

Inhibiting glutamine metabolism is a critical component of a combination regimen with immune checkpoint blockade. After activation, effector T cells and cancer cells, can undergo glutamine anaplerosis as a result of increased Myc expression in response to TCR stimulation.(258) This upregulates the glutamine transporter SLC1A5, and lead to glutamine addiction to fuel the TCA cycle.(259) *In vitro* and *in vivo*, genetic inhibition of GLS decreases T cell activation and impairs Th17 differentiation. However, transient pharmacologic inhibition of GLS results

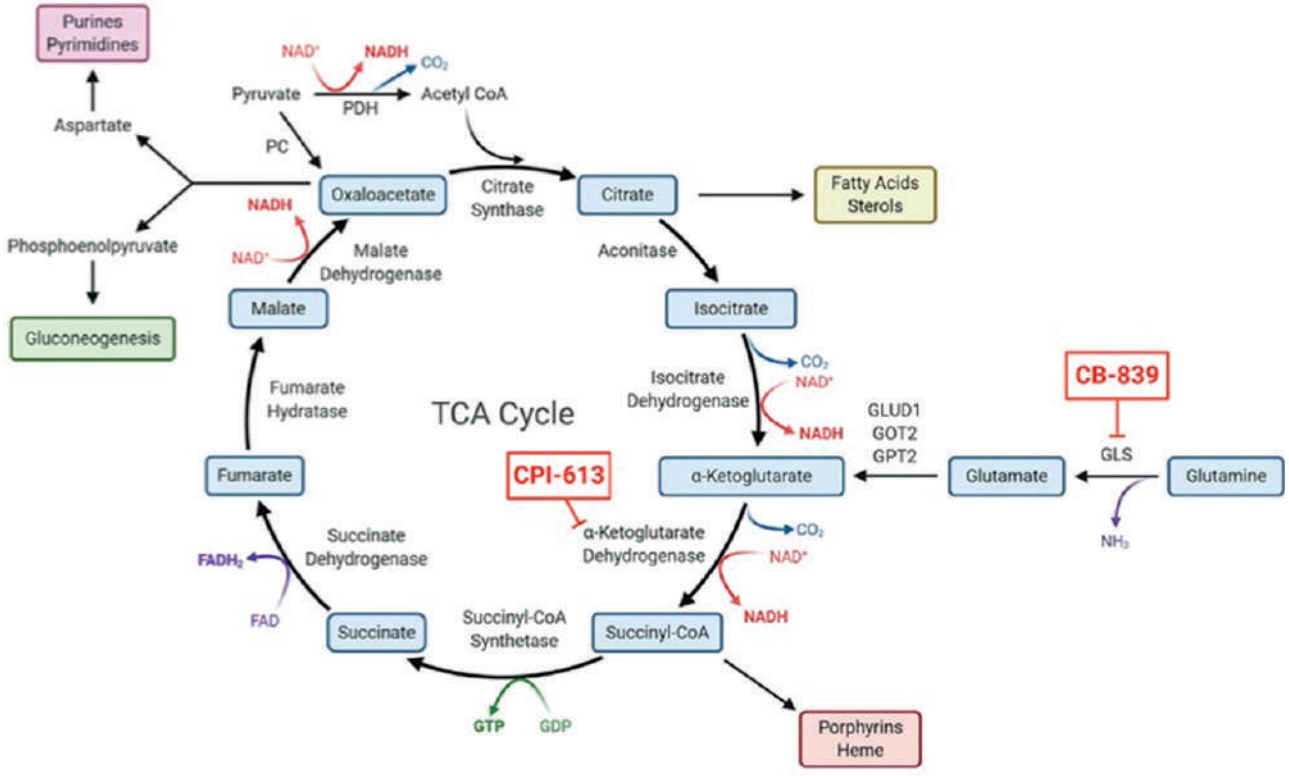

Figure 6. TCA cycle feeds multiple biosynthetic pathways.(214) (Adapted with persmission from Elsevier).

in an increase in Th1 and cytotoxic T lymphocyte (CTL) counts, as well as enhanced anti-tumor immune responses. JHU083, a prodrug for the glutamine antagonist 6-diazo-5-oxo-L-norlecuine (DON), is activated in the tumor microenvironment and increases T cell mitochondrial metabolism, promoting anti-tumor immune responses.(260) It will be interesting to see whether inhibiting glutamine metabolism is effective in patients who do not respond well to immune checkpoint blockade in the future. Additionally, the mechanism by which other mitochondrial metabolism inhibitors, such as CPI-613, impair immune responses remains unknown.

Metabolic Control Of Epigenetics In Cancer

Metabolites can act as regulator for epigenetic modification, involving acetyl-CoA followed by a line of subcellular compartmentalization of metabolic pathways. Oncogenic metabolic rewiring has a detrimental effect on acetyl-CoA production and histone acetylation in cancer cells (Figure 7). Acetyl-CoA is a primary target of metabolic rearrangement in cancer cells, therefore many cancer driver mutation or primary molecular changes impact directly on acetyl-CoA homeostasis suggests a close relationship between molecular and metabolic signaling.(14)

Epigenetic information is critical for the regulation of all DNA-dependent processes, including transcription, DNA repair, and replication. As a result, any genomic modification can impact not only on cell homeostasis but also initiating cancer.(261) Epigenederegulation can also occur prior to transformative genetic events, such as mutations in tumor suppressors and/or proto-oncogenes, as well as genomic instability.(261,262) Additionally, some studies demonstrated that cancer is a repository of recurrent somatic mutations in a variety of epigenetic regulators.(261)

Cytosine methylation in a high density of CpG sites (CpG islands) areas, which are primarily found in promoter regions, is strongly associated with transcriptional silencing. (263) Methyl group additional to cytosine is catalyzed by DNA methyltransferases (DNMT1, DNMT3a, and DNMT3b) using the methyl donor SAM. During replication, DNMT1 preferentially methylates the unmethylated strand

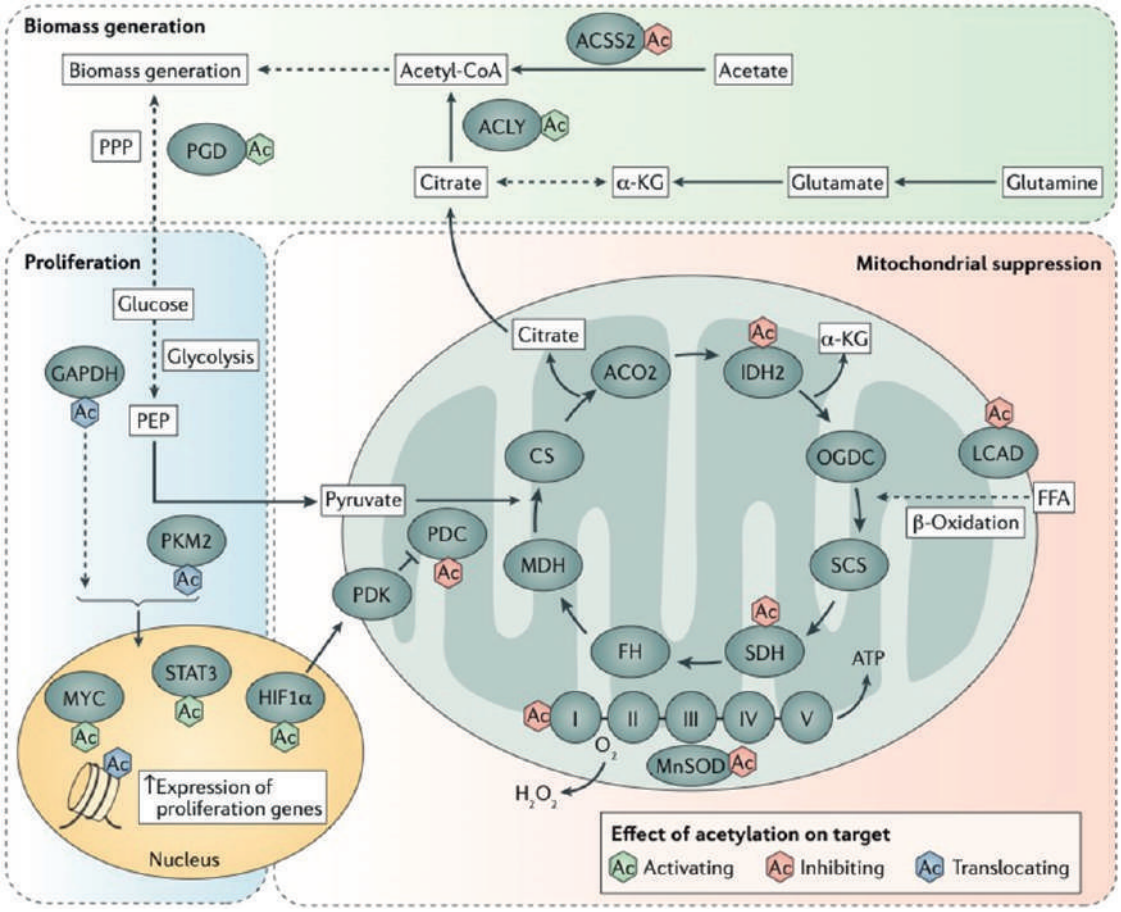

Figure 7. Acetylation promotes molecular and metabolic rewiring in cancer.(14) (Adapted with permission from Macmillan Publishers).

of hemi-methylated DNA, whereas DNMT3a and DNMT3b catalyze *de novo* methylation in both strands.(264) DNA demethylation is accomplished through the oxidation of 5mC, which is catalyzed by enzymes of the ten-eleven translocation protein (TET) family.(265)

CpG islands are largely unmethylated in normal cells, whereas CG-deficient regions within gene bodies are highly methylated. These patterns changed in numerous cancer where CpG island become hypermethylation while gene bodies were hypomethylated.(263) The most well-known epigenetic alteration in human cancers is CpG island promoter hypermethylation-associated silencing of tumor suppressor genes such as cyclin dependent kinase inhibitor 2A (CDKN2A), MutL homolog 1 (MLH1), Breast cancer type 1 (BRCA1), and Von Hippel–Lindau syndrome (VHL), which has been identified as a driver of lung, colorectal, breast, and renal cancer progression.(10,186) CDKN2A methylation has been associated with increased SET domain bifurcated histone lysine methyltransferase 1 (SETDB1) expression and, consequently, uncontrolled tumor cell proliferation (279), and the well-known MLH1 promoter hypermethylation in colorectal cancers appears to be the result of increased H3K9me3 levels caused by LSD1 activity, which favors glycolytic metabolism under hypoxic conditions.(266)

CpG island promoter hypermethylation-associated silencing of tumor suppressor genes such as CDKN2A, MLH1, BRCA1, and VHL, which has been identified as a driver of lung, colorectal, breast, and renal cancer development, is the most well-known epigenetic change in human malignancies.(10,188) Increased H3K9me3 levels caused by LSD1 activity, which favors glycolytic metabolism under hypoxic conditions, have been linked to increased CDKNA methylation and, as a result, uncontrolled tumor cell proliferation.(267) The well-known MLH1 promoter hypermethylation in colorectal cancers appears to be the result of increased H3K9me3 levels caused by LSD1 activity, which favors glycolytic metabolism under hypoxic conditions.(268)

Epigenetic mechanisms regulate gene expression in a highly adaptable manner to environmental factors.(269) As cancer cells divide, acquired epigenetic states can be maintained via DNA methylation, repressive chromatin, or gene regulatory circuits, resulting in the formation of adaptive epi-clones that promote malignant progression. (270) Molecular changes associated with metabolic reprogramming are required during cancer initiation and/or progression to meet cancer cells' energy demands, which are frequently coordinated with increased biosynthetic processes and energy production (3), a recognized cancer hallmark.(11)

The altered metabolic reprogramming including lipid biosynthesis reprogramming (118), and the Warburg effect contributes to the production of antioxidant glutathione, which neutralizes reactive oxygen species and protects cells from oxidative stress.(31) Thus, the interaction of metabolomics and epigenetics promotes neoplastic transformation by supporting several malignant traits. Although a comprehensive understanding of the epigenetic and metabolic interactions in cancer is far from complete, conceptual frameworks are beginning to emerge.(268)

One example where epigenetic alteration affect the deregulation of metabolic enzymes in cancer cells is the overexpression of hexokinase 2 (HK2) in liver cancer and glioblastoma, where the promoter hypomethylation promotes glycolytic flux.(9,271,272) Additionally, the activity of acetylated PKM2 is decreased at the final glycolysis step, increasing the availability of glycolytic intermediates for the biosynthesis of nucleic acids, lipids, and amino acids required for tumor cell proliferation.(273) Certain metabolites have an effect on the fate of cancer cells, resulting in gene deregulation in cancer cells and also in the tumor microenvironment.(274)

Metabolic reprogramming in cancer has a significant effect on the epigenetic machinery. The tumor cells Warburg effect enables them to utilize lactate and glycolytic metabolites, as HDAC inhibitors promote hyperacetylation of genes involved in cell proliferation. Certain metabolites have the ability to promote tumorigenesis by altering the epigenome; these metabolites are referred to as oncometabolites.(275) Mutations in enzymes involved in the TCA cycle cause oncometabolites such fumarate, succinate, and 2-hydroglutarate (2-HG) to be generated in excess. The buildup of metabolites caused by mutations in metabolic enzyme genes can influence histone and DNA methylation. AML, lymphoma, glioblastoma, and chondrosarcoid cancers have all been linked to IDH1 and IDH2 mutations.(276-278) IDH1/2 loss-of-function mutations prevent the conversion of α-ketoglutarate to isocitrate, thereby favoring the synthesis of 2-HG.(279) This oncometabolite is competitive inhibitor of α-ketoglutarate, inhibiting TET and JmjC activity.(280) 2-HG is produced by malate dehydrogenases 1 and 2, as well as Lactate dehydrogenase A (LDHA). It is higher in breast and renal malignancies and has been linked to MYC activation and L-2-hydroxyglutarate dehydrogenase insufficiency in renal and breast cancer.(281) Several innovative cancer treatments targeting tumor metabolism to correct epigenetic dysregulation and epigenetic-modifying

medications, aim to influence cancer metabolism, due to the complex link between epigenetics and metabolism.

Increased histone acetylation in cancer cells is partly a result of increased glycolytic flow (and associated glucose flux), which is mediated by acetyl-CoA and citrate. Thus, inhibiting glycolysis may have an effect on histone acetylation. 2-Deoxyglucose (2-DG), a glucose analog, may inhibit G6P production competitively, thereby impeding the glycolytic pathway.(267) Moreover, 2-DG treatment in cancer cell lines decrease acetyl-CoA levels, thus lower the histone H3 and H4 levels. It suggested to interfere the DNA repair mechanism so the cancer cells are more vulnerable to DNA-damaging agents.(282) 3-bromopyruvate, another glycolysis inhibitor, reduces acetyl-CoA and induces differentiation in embryonic stem cells.(283)

Numerous inhibitors of GLS, the enzyme that converts glutamine to glutamate, have been developed. Two GLS inhibitors are compounds 968 and CB-839. Reduced expression of several cancer-associated genes was observed in breast cancer cells as a result of 968-induced changes in H3K4 methylation and H4K16 acetylation (284), whereas CB-839 is currently in Phase I trial in solid and hematological cancers (285,286). IDH mutations are critical events in leukemias and gliomas' epigenetic landscapes. Inhibition of IDH1/2 has been proposed to inhibit 2-HG production. AGI-5198 was shown to inhibit 2-HG production and cell growth in mutant IDH glioma cells, while inducing H3K9me3 and H3K27me3 demethylation and having no effect on DNA methylation.(287) The same result was reported in human IDH mutant chondrosarcoma cells.(288) Subsequently, novel inhibitors of mutant IDH1R132H have demonstrated efficacy, including AG-120, AG-881, ML309, GSK321 and GSK864.(271) Additionally, AG-221, a first-in-class inhibitor of mutant IDH2, improves survival in primary human IDH2 mutant AML xenografts. (272) This IDH2 inhibitor was evaluated in Phase I and Phase II clinical trials, where it demonstrated significant reductions in 2HG levels in bone marrow and plasma, and give benefits for patients with IDH mutation.(271) Another IDH2 inhibitor, AGI-6780 act as an epigenetic deregulation by histone demethylation and reversing gene expression patterns acquired during tumorigenesis.(273)

Finally, altered metabolism and epigenetic deregulation both contribute to cancer cells' adaptation to an ever-changing environment. In cancer cells, metabolic rewiring alters the epigenome, facilitating tumor development and progression. Specifically, acetyl-CoA pools which play a critical role in epigenetic regulation. Histone acetylation patterns in various transcriptional gene targets may be activated depending on the metabolic pathway involved in acetyl-CoA production. Combining epigenetic and metabolic targeting may result in a more effective method of tumor progression inhibition. In general, given the critical role of the tumor microenvironment in epigenetic plasticity, patients may benefit from the addition of additional therapeutic strategies that target TME components (*e.g.*, anti-angiogenics, immune checkpoint inhibitors) to standard chemotherapy. Taken together and theoretically, these combinations are likely to have a beneficial effect on the management of cancer patients.(268)

Targeting Bioenergetic Pathways in Gliomas

After all theories we discussed above, we will take an example from glioma metabolism pathways. Gliomas are primary central nervous system tumors that arise from the brain's intrinsic constituent cells.(289,290) Glioblastoma (GBM) is the most aggressive ana lethal subtype of glioma in adults.(291) Recent advances in integrating metabolomics and genomics providing new insight into the pathogenesis of gliomas and the interactions between the tumor microenvironment and the tumor genotype, providing critical insight into how gliomas respond to and adapt to changing tissue and biochemical contexts.(292)

Two of the most prevalent nutrients in the brain are glucose and acetate (293), and they are readily assimilated by tumor cells. Glioma cells, like many other types of cancer, exhibit rapid glucose uptake from the microenvironment and accelerated glycolysis (the 'Warburg' effect) in order to generate enough ATP to fuel cellular reactions (216,291, 294).

This metabolic adaptation, which is not always observed in tumors, is just the beginning. This metabolic adaptability is only the beginning. Glioma cells increase internal lipid, amino acid, and nucleotide reserves by a number of molecular processes, either by extracellular absorption, *de novo* synthesis, and carbon and nitrogen flow through various routes.(215,294) Both the tumor's genetics and the biochemical microenvironment appear to influence these metabolic changes.

Another most obvious signals emerging from multiple independent sequencing efforts (296,297) is the high frequency of growth factor signaling pathways alteration (particularly in GBMs) to control metabolic flux (291,295,296) and the recurrence of mutations in the genes

encoding IDH1 and IDH2 (276,296), which are components of the tricarboxylic acid cycle.

GBM cells can use both glycolysis and OXPHOS in the mitochondria during aggressive tumor development. (297) Acetyl-CoA may be produced in the mitochondria from pyruvate via pyruvate dehydrogenase (PDH) or FA oxidation, forming a metabolic connection between the mitochondrial TCA cycle and cytosolic metabolite pools or in the cytosol from citrate via ACLY.(298) These observed in mice and also in patients with GBM or in patient-derived by 13C nuclear magnetic resonance (297), that the majority of acetyl-CoA is not come from glucose, but non-glucose carbon sources which contribute to GBM bioenergetics. Glioma cells also inhibit the growth of glioma tumors in GBM xenograft models by blocking key enzymes such as FASN (299), and fatty acid elongase 2 (ELOVL), thus, FA are needed for the cell's survival (300,301).

The molecular mechanism behind glioma-related changes in nutrition absorption and utilization is yet unclear. Glioma metabolism has been linked to frequent amplification of genes encoding growth factor RTK and IDH mutations. TP53 mutations are common in low-grade gliomas (302), including those that proceed to GBM; MDM2 and MDM4 amplification, which can mimic certain elements of p53 loss (303).

Myc has been identified as a critical regulator of altered glioma metabolism.(304,305) Myc's role in glucose transport, glycolysis, glutaminolysis, lipogenesis, and nucleotide synthesis has been well established for a long period of time.(306) However, the role of Myc, which was discovered relatively recently. Myc in GBM promotes the expression of glucose transporter GLUT1, HK2, muscle phosphofructokinase (PFKM), and enolase 1 (ENO1) genes, raises glycolytic flux, and glutamine levels.(307-309) It also has recently been demonstrated that to stimulate NAD^+ production via the salvage route via an epigenetic mechanism, causing a reliance and addiction to critical metabolites.(310)

Landscape of common targetable mutations in protein-coding genes has been extensively explored in malignant gliomas.(276,295) However, pharmacokinetic and difficulty of incorporating ecDNA-based amplification challenges

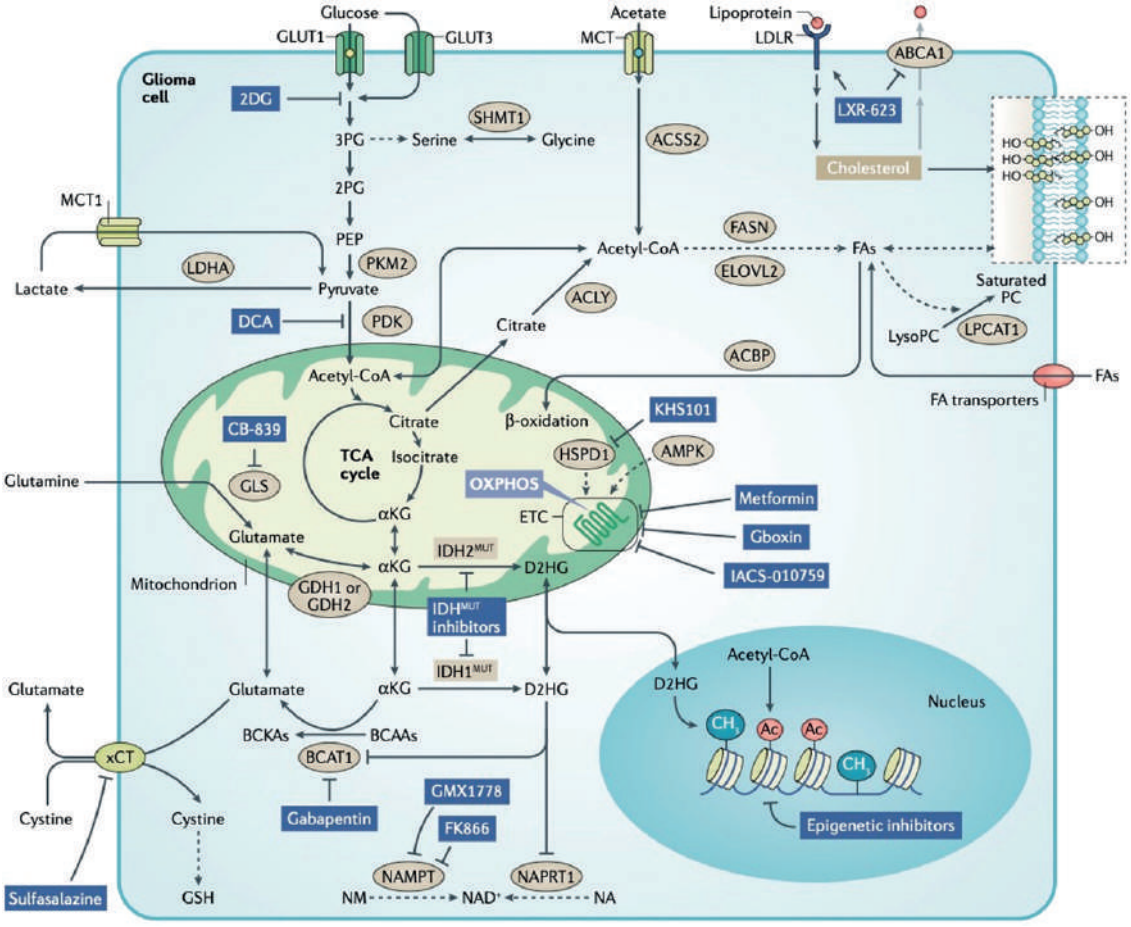

Figure 8. An expanded pharmacopoeia of metabolic drug targets in malignant glioma.(292) (Adapted with permission from Springer Nature).

(304,311) to translate the genomic strategies into successful therapies. Over the last decade, studies shedding new light on glioma metabolic reprogramming have suggested that identifying actionable metabolic dependencies in gliomas, such as potential metabolic biomarkers and therapeutic targets, may aid in the development of novel glioma treatment strategies (Figure 8).

Several examples of previously unanticipated targets have been identified as a result of these types of integrated analyses to date, such as critical enzymes involved in the acetyl-CoA and FA synthesis pathways, such as ACLY (312,313), Acyl-coenzyme A synthetase short-chain family member 2 (ACSS2) (314,315), FASN49, ELOVL2 (301) and acyl-CoA binding-protein (ACBP) (299), have been identified as potential drug targets for gliomas driven by RTKs or EGFRs. Recent research suggests that tissue lineage influences NAD biosynthetic pathway dependency, and that GBMs establish an epigenetic dependence on nicotinamide Phosphoribosyltransferase (NAMPT) for NAD biosynthesis in a Myc- and MAX-dependent manner (316,317).

The metabolic state of malignant gliomas is dynamic. In the last decade, malignant glioma research has advanced to the forefront of science, owing to the elucidation of several critical mechanisms of tumor metabolic reprogramming. It is past time for some of this knowledge to be applied clinically for the benefit of patients.

Conclusion

Extensive research on the Warburg Effect and its functions in cancer cells has advanced our understanding of the mechanism why it occurs and what conditions are necessary for tumor cell proliferation. Mitochondrial metabolism has play critical roles in cancer development and together immunometabolism, and histone modification result in oncogenes metabolic alteration. In cancer, metabolic rewiring alters the epigenome in a way that promotes tumor development and/or progression. Expanding our understanding of how metabolic enzymes affect epigenetics and cell fate decisions has the potential to result in novel cancer therapies.

Authors Contribution

AM writing and revising manuscript, NMD crosschecking and editing manuscript, AW concepting the idea and supervising.

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