

Dysregulated metabolic enzymes and metabolic reprogramming in cancer cells (Review)

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Abstract. Tumor cells carry various genetic and metabolic alterations, which directly contribute to their growth and malignancy. Links between metabolism and cancer are multifaceted. Metabolic reprogramming, such as enhanced aerobic glycolysis, mutations in the tricarboxylic acid (TCA) cycle metabolic enzymes, and dependence on lipid and glutamine metabolism are key characteristics of cancer cells. Understanding these metabolic alterations is crucial for development of novel anti-cancer therapeutic strategies. In the present review, the broad importance of metabolism in tumor biology is discussed, and the current knowledge on dysregulated metabolic enzymes involved in the vital regulatory steps of glycolysis, the TCA cycle, the pentose phosphate pathway, and lipid, amino acid, and mitochondrial metabolism pathways are reviewed.

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1. Introduction

Metabolic alteration is a hallmark of cancer cells (1). A growing body of evidence indicates that malignant transformation is

characterized by the occurrence of multiple changes in metabolic pathways that are linked to the synthesis of macromolecules (2). Metabolism is the fundamental architecture of cellular life. Typically, every cell in the body, either directly or indirectly, undergoes metabolism. Metabolism is a sum or a collection of biochemical reactions that produce energy for vital processes and for synthesizing macromolecules. Unsurprisingly, mitochondria, the power house of cells, perform a central role in energy metabolism. Either because of a direct impact or its pivotal role in signal transduction, mitochondria are hubs for metabolic alterations and reprogramming. Furthermore, mitochondria are involved in the production of adenosine triphosphate (ATP), and exert key roles in redox regulation, calcium homeostasis, cell signaling, cell death, and production of various intermediates that are necessary for macromolecule synthesis (3-6).

Increasing attention has been given to the role of mitochondrial metabolism in cancer biology. The complex connection between metabolism and tumorigenesis is a promising area of cancer research. Mounting evidence has demonstrated that targeting mitochondrial metabolism in cancer cells may present as a novel strategy for anti-cancer therapy (7-11). As summarized from current knowledge, the process of tumorigenesis and mitochondrial biology intercross at multiple levels as follows: i) Direct signals from mitochondria promote tumorigenesis; ii) oncogenic signaling pathways alter mitochondrial functions; iii) perturbation of mitochondrial functions have been shown to have a major role in regulating metabolism and bioenergetics; iv) mutations in mitochondrial DNA, proteins and enzymes result in altered levels of metabolites, which support tumor development and progression. The current review focuses on the importance of various such classic alterations in cancer metabolism. Hence, by understanding this aspect of metabolism, cancer biology may be better understood and novel anti-cancer drugs may be developed.

2. Glycolysis

All parts of the body require energy to work and this energy is derived from consumption of food. Typically, all food is broken down into smaller parts to generate the energy source, ATP. ATP is a chemical energy generated via controlled oxidation of glucose and other molecules. The process of the breakdown

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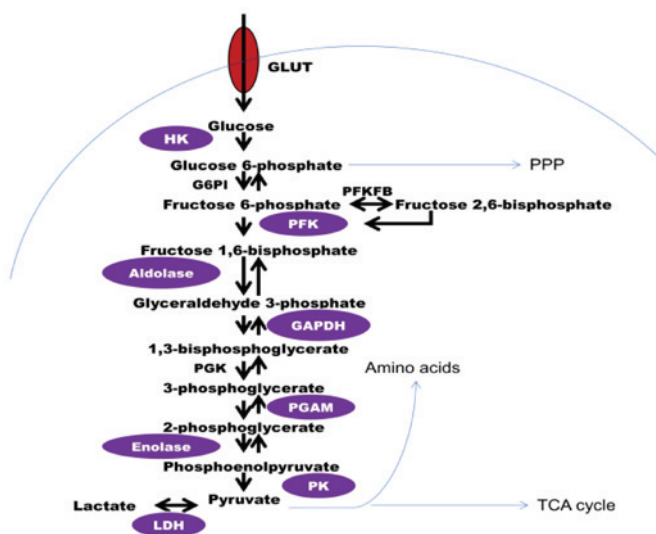


Figure 1. Glucose metabolism. Glycolysis is the catabolic process in which glucose is broken down to pyruvate via these 10 enzymatic steps. Numerous glycolytic enzymes are altered in cancer cells (purple ovals). GLUT, glucose transporter; HK, hexokinase; PPP, pentose phosphate pathway; PFKFB, 6-phosphofructo-2-kinase/fructose 2,6-bisphosphatase; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; PGAM, phosphoglycerate mutase; PK, pyruvate kinase; LDH, lactate dehydrogenase; TCA, tricarboxylic acid cycle.

of glucose, termed glycolysis, occurs in the cytoplasm of mammalian cells. Glucose from food is taken up by specific glucose transporters in the cell surface, and via a series of enzyme-catalyzed reactions, broken down to pyruvate, the end-product of glycolysis under aerobic conditions (Fig. 1). If there is a lack of oxygen supply, pyruvate is converted to lactate (anaerobic glycolysis). Theoretically, one molecule of glucose yields two molecules of pyruvate and two molecules of ATP via glycolysis.

Since the early twentieth century, abnormalities of glycolysis in cancer cells have been observed. Warburg (12), a German physiologist and a Nobel laureate, observed that tumor cells depend solely on glycolysis for energy production, even with an ample quantity of oxygen. This phenomenon is since termed the Warburg effect of cancer cells. This raises the question as to why cancer cells switch their metabolism to aerobic glycolysis, unlike normal cells, which depend on oxidative phosphorylation for energy production. While the exact reasons remain unclear, the current explanations include: i) Aerobic glycolysis, although less efficient than the classic oxidative phosphorylation, provides rapid supply of ATP; ii) glycolysis intermediates provide sufficient building blocks for macromolecule synthesis required for the enhanced cell proliferation. Due to this feature of cancer cells, studies have been focused on novel strategies to selectively inhibit glucose metabolism and/or glucose transport in cancer cells (13-16).

Marked progress has been made in understanding the molecular mechanisms leading to constitutive upregulation of glycolysis in tumor cells. Various glycolytic enzymes are multifunctional proteins whose expression levels are often increased in cancer cells. For example, hexokinase (HK), the enzyme that converts glucose to glucose 6-phosphate (G6P), the first step of glycolysis, is involved in transcription regulation, and its expression is often upregulated in tumor cells (17,18). The

majority of malignant cells display enhanced expression levels of type II isoform (HK-II), which may contribute to the elevated glycolysis (19,20). Phosphofructokinase (PFK), the enzyme that catalyzes the rate limiting step of glycolysis, has been identified to be upregulated in types of breast cancer (21,22). Another critical regulator of glycolysis is the enzyme 6-phosphofructo-2-kinase/fructose 2,6-bisphosphatase (Pfkfb), a family of bifunctional enzymes that control the levels of fructose 2,6-bisphosphate, which in turn is a powerful allosteric activator of PFK1. Two Pfkfb isoforms, type 2 and 3, are associated with cancers (23-26). Subsequently, the enzyme aldolase that catalyzes the reversible conversion of fructose-1,6-bisphosphate to glyceraldehyde-3-phosphate and dihydroxyacetone phosphate, has been demonstrated to be overexpressed in squamous cell lung carcinoma (27). The well-known classic glycolytic enzyme, glyceraldehyde-3-phosphate dehydrogenase (GAPDH; the housekeeping gene) is also implicated in cancer. Overexpression of GAPDH is considered an important feature of numerous types of cancer (28-30). GAPDH has been proposed as a promising target for the treatment of carcinomas (31). Pyruvate kinase (PK), the enzyme that catalyzes the irreversible phosphoryl group transfer from phosphoenolpyruvate to pyruvate, yielding pyruvate and ATP, appears to be involved in cancer; previous studies and our findings have demonstrated that tumor cells overexpress the type M2 isoform, PKM2 (32-35). As the majority of cancer cells are dependent on aerobic glycolysis for ATP production, the enzyme, lactate dehydrogenase (LDH), which catalyzes the conversion of pyruvate to lactate, is the key to determining the glycolytic phenotype of cancer cells. Thus, LDH is a promising target for anti-cancer therapy. The inhibition of LDH suppresses tumor progression of lymphomas and pancreatic cancer xenografts (36). These results indicate that selectively targeting glycolysis and/or glycolytic enzymes in tumor cells may present as an effective approach for the treatment of different types of cancer.

3. Tricarboxylic acid (TCA) cycle

The Krebs cycle (the citric acid cycle or the TCA) is a series of chemical reactions that generate energy via the oxidation of pyruvate (Fig. 2). TCA cycles occur in all aerobic living organisms. It provides precursors for biosynthesis of compounds (such as amino acids), and nicotinamide adenine dinucleotide (NADH), which is later used by the electron transport chain to generate energy by converting NADH to NAD⁺. The TCA cycle is the central metabolic hub of the cell that occurs primarily in the mitochondria in contrast to glycolysis, which occurs in the cytosol. Even a minor alteration in these processes markedly influences mitochondrial energy production. Although mutations in mitochondrial DNA have been evaluated for over two decades (37-39), much attention has been focused on the identification of mutations in various TCA cycle enzymes (40,41). The cycle consists of eight steps catalyzed by eight different enzymes. Mutations in genes that encode enzymes aconitase, isocitrate dehydrogenase (IDH), succinate dehydrogenase (SDH), and fumarate hydratase (FH) may lead to cancer. Aconitase catalyzes isomerization of citrate to isocitrate via cis-aconitase. Altered expression levels of aconitase are implicated in human prostate cancer, wherein the normal citrate-

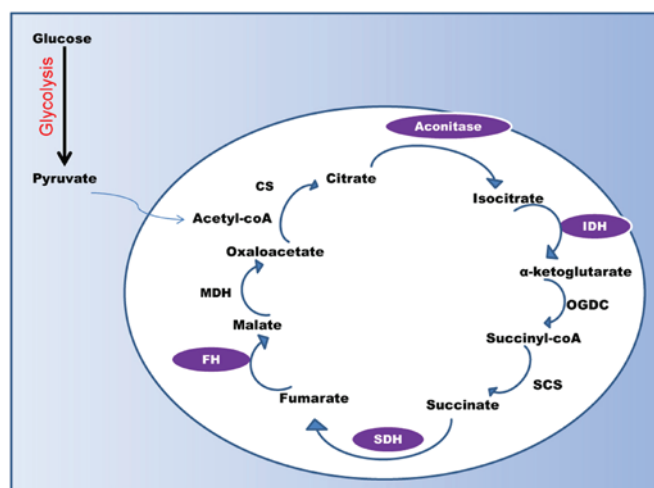


Figure 2. Krebs cycle. The TCA is comprised of series of enzyme-catalyzed reactions, located in the mitochondrial matrix. Various enzymes (purple ovals) of the TCA cycle are mutated and/or altered in many types of cancer. TCA, tricarboxylic acid cycle; IDH, isocitrate dehydrogenase; OGDC, oxoglutarate dehydrogenase complex; SCS, succinyl-CoA synthetase; SDH, succinate dehydrogenase; FH, fumarate hydratase; MDH, malate dehydrogenase; CS, citrate synthase.

producing glandular secretory epithelial cells undergo a metabolic transformation to malignant citrate-oxidizing cells, leading to abnormal citrate metabolism and prostate malignancy (42). IDH converts isocitrate to α -ketoglutarate (α -KG). Glioblastoma multiforme, one of the most common and lethal types of brain cancer, is characterized by IDH1 gene mutations (43). Similar studies discovered mutations in IDH1 and IDH2 genes in the pathogenesis of malignant gliomas (44). Mutations that occur in single amino acid residue of IDH1 active sites not only result in the novel ability for the mutant enzyme to convert α -KG to 2-hydroxyglutarate, which is proposed to contribute to the formation and malignant progression of gliomas (45). FH is the enzyme that converts fumarate to malate, and mutations in the FH gene are associated with cutaneous, uterine and aggressive forms of renal cancer (46-48). Cancer cells that harbor FH mutations produce up to 100-fold more fumarate, and seven-fold more succinate, but decreased levels of citrate and malate (49). FH deficiency in tumor cells alters redox homeostasis to promote tumorigenesis (48). Mutations in the enzyme SDH, which catalyzes the oxidation of succinate to fumarate, are implicated in pheochromocytoma, paraganglioma, renal cell carcinoma and papillary thyroid cancers (50-52). Reduced expression and loss of heterozygosity of the SDH gene are observed in gastric and colon carcinoma (53). SDH downregulation results in succinate accumulation leading to transmission of an oncogenic signal from mitochondria to the cytosol (54).

4. Pentose phosphate pathway (PPP)

The PPP, which branches out from glycolysis at the first committed step is the major catabolic pathway of glucose for nucleotide synthesis in cancer cells (55-57). The conversion of glucose to G6P, which is catalyzed by the enzyme HK, is a common precursor for various metabolic glucose-consuming routes (Fig. 3). Through this pathway, cancer cells produce large quantities of ribose-5 phosphate (a precursor for nucleotide

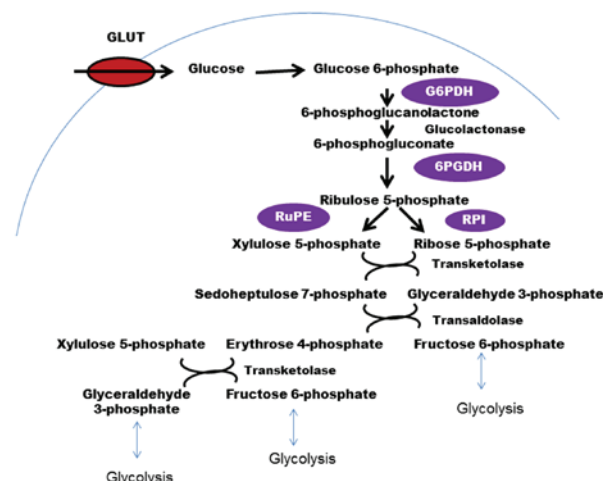


Figure 3. PPP, which branches out from glycolysis at the first committed stage of glucose metabolism, is required for nucleotide synthesis in cancer cells. Numerous enzymes of the PPP are associated with various types of cancer. PPP, pentose phosphate pathway; GLUT, glucose transporter; G6PDH, glucose 6-phosphate dehydrogenase; 6PGDH, 6-phosphogluconate dehydrogenase; RuPE, ribulose-5-phosphate-3-epimerase; RPI, ribose-5-phosphate isomerase.

synthesis) and NADPH (a cofactor used in anabolic reactions). PPP runs parallel to glycolysis and activation of these signaling pathways is a common hallmark of tumor cells (58,59). As cancer cells are rapidly dividing, the cells require a constant supply of nucleotides, and the majority of the pentose phosphates are derived from the PPP. Thus, PPP may influence the glycolytic flux. Various enzymes that execute the PPP are implicated in different types of cancer. G6P dehydrogenase (G6PD or G6PDH), the enzyme that catalyzes the rate-limiting step in the PPP, and generates the first NADPH, is highly overexpressed in certain tumors (60). Elevated levels of G6PD in association with higher levels of PPP-derived metabolites are responsible for clear-cell renal carcinoma-associated metabolic alterations (61). Overexpression of G6PD in human U2OS bone osteosarcoma epithelial cells enhances the PPP-dependent production of NADPH (62). The same group also demonstrates that simultaneous inhibition of glycolysis and PPP using 2-deoxy-d-glucose and 6-aminonicotinamide, respectively, induces oxidative stress and sensitizes malignant human cancer cell lines to radiotherapy, presumably via the induction of multiple cell death modalities, including apoptosis, necrosis and mitotic catastrophe (63). The next enzyme that has a role in cancer is 6-phosphogluconate dehydrogenase (6PGDH). 6PGDH catalyzes the oxidative decarboxylation of 6-phosphogluconate to ribulose 5-phosphate with a reduction of NADP to NADPH. 6PGDH has been shown to be critical for lung carcinogenesis and its inhibition may be a novel strategy to treat glycolytic lung tumors (55). Ribulose-5 phosphate isomerase, another critical enzyme in the PPP, which catalyzes the conversion of ribulose-5 phosphate to ribose-5 phosphate and xylulose-5 phosphate (Xu5P), is also associated with cancer (55). Ribose-5 phosphate is important as it is a precursor for *de novo* nucleotide synthesis in rapidly proliferating cancer cells. Xu5P increases the levels of PFKFB, which activates PFK1 and increases glycolytic flux (64). Thus, all of these studies implicate that the regulation of PPP is vital for cancer cell survival and proliferation. Furthermore, increased

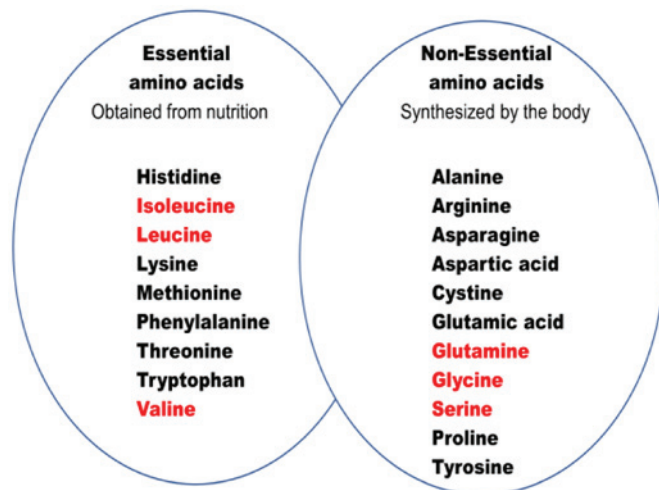


Figure 4. Essential and non-essential amino acids.

glycolytic flux in cancer cells may be regulated directly or indirectly by PPP, and hence, this may represent a promising strategy for treatment of cancer cells.

5. Amino acid metabolism

Amino acids are one of the major fuels for biosynthetic reactions (Fig. 4), and therefore, are intricately involved in cellular metabolism. From the above-mentioned studies, it is evident that cancer cells are characterized by altered metabolism and/or dysregulated metabolic pathways. Amino acids are of utmost necessity for cancer cell proliferation, as they are the major source of nutrients. Even a slight alteration in the biosynthetic pathways may have an impact on amino acid synthesis. Despite glutamine being a nonessential amino acid, it is one of the major fuels for cancer cells (65-67). In cancer cells, glutamine is a primary mitochondrial substrate required to maintain mitochondrial membrane potential, integrity and for NADPH production (65). Certain tumor cells are characterized by 'glutamine addiction', the ability of cancer cells to exhibit a high rate of glutamine uptake. Glutamine catabolism or glutaminolysis is elevated in certain types of tumor (68-70). Enzyme glutaminase converts glutamine to glutamate and ammonia. Glutamate is further converted to α -KG and enters the TCA cycle. Emerging evidence indicates the role of glutamate and glutamate receptors in human rhabdomyosarcoma/medulloblastoma (TE671), neuroblastoma (SK-NA-S), thyroid carcinoma (FTC 238), lung carcinoma (SK-LU-1), astrocytoma (MOGGCCM), multiple myeloma (RPMI-8226), glioma (U87-MG and U343), lung carcinoma (A549), colon adenocarcinoma (HT 29), T cell leukemia cells (Jurkat E6.1), breast carcinoma (T47D) and colon adenocarcinoma (71). Glutamine is also involved in activating mechanistic target of rapamycin complex 1 (68,72). Glycine, another nonessential and one of the simplest amino acids, has also been implicated in cancer (73,74). Glycine is a significant constituent of proteins in the body, which build tissues and organs. It is the most abundant type of amino acid in the body and one of the most important regulators of inflammation (75-77). Glycine metabolism has also been demonstrated to be upregulated in non-small cell lung cancers (74,78). Studies have demonstrated

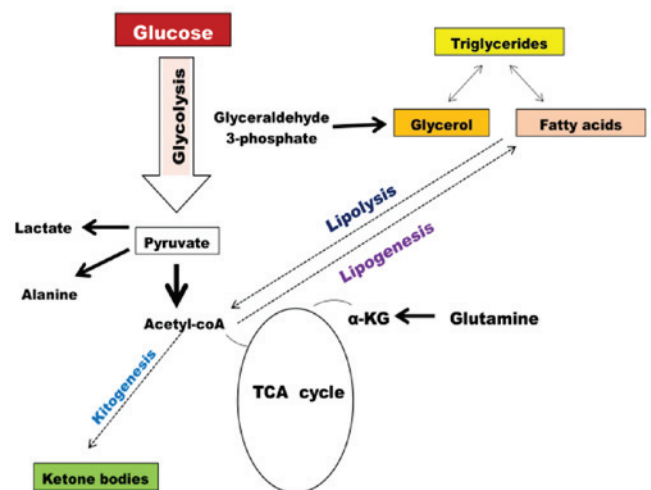


Figure 5. Lipid metabolism. The interactions between glycolysis, Krebs cycle and lipid metabolism. Lipogenesis is the formation of lipids, whereas lipolysis is the breakdown of lipids. Triglycerides are made up of glycerol and fatty acids. Fatty acids undergo β -oxidation producing acetyl CoA, which enters the TCA cycle. TCA, tricarboxylic acid cycle; α -KG, α -ketoglutarate.

that glycine stimulates proliferation of tumor cells, and cancer cells deprived of glycine indicated a significant reduction in cell growth (74,79). Serine, another important nonessential amino acid that participates in nucleotide synthesis, has been shown to be upregulated in breast cancer (74,80). Studies using melanoma cells have demonstrated that significant portions of serine are converted to glycine (81). Serine, glycine, and folate (vitamin B9) are constitutively active in various tumor cells (74,79,82).

6. Lipid metabolism

The role of lipid metabolism in cancer cells has long been disregarded; over the past decade, the increased rate of lipid metabolism in cancer cells is being recognized as the prominent hallmark of transformed cells (83-85). Lipids are a diverse group of molecules composed of fat, triglycerides, phospholipid, cholesterol and cholesterol esters (Fig. 5). Lipids form the major component of cell membranes (phospholipid bilayer), hormones (steroid hormones, such as cholesterol) and certain lipid-soluble vitamins. Hence, lipids perform various roles in the body, from providing energy to muscles to producing hormones (86). In rapidly proliferating cancer cells, there is an overwhelming requirement for macromolecule synthesis. Hence, cancer cells also demonstrate a high dependence on lipids (83). One of the enzymes involved in the synthesis of *de novo* fatty acids is ATP citrate lyase (ACLY). ACLY catalyzes the conversion of mitochondrial-derived citrate to oxaloacetate and cytosolic acetyl-CoA. Thus, ACLY links *de novo* lipogenesis to gluconeogenesis and the Krebs cycle (87). Studies have demonstrated that higher expression levels of ACLY correlated with advanced stages of cancer and lymph node metastasis in tissue samples from gastric adenocarcinoma patients (88). However, targeting ACLY by microRNA-22 (miR-22) suppresses cancer cell proliferation and invasion in osteosarcoma, prostate, cervical and lung cancer cells (89). Another study demonstrates that ACLY is

required for low molecular weight isoform of cyclin E mediated transformation, migration, and invasion of breast cancer cells *in vitro* along with tumor growth *in vivo* (90). Acetyl-CoA carboxylase (ACC) is the rate-limiting enzyme in fatty acid synthesis. ACC carboxylates acetyl-CoA to form malonyl-CoA. In patients with squamous cell carcinoma of the head and neck, there is an association between phosphorylated AMP-activated protein kinase and ACC expression, and the therapeutic outcome is that high phosphorylated-ACC expression is associated with a worse overall survival rate in the patients (91). Similarly, ACC1 expression is upregulated in patients with hepatocellular carcinoma (HCC), and upregulation of ACC1 is also significantly correlated with the poorer overall survival of, and disease recurrence in HCC patients (92). Fatty acid synthase (FASN), which catalyzes the final step in fatty acid synthesis, is often overexpressed in human cancers (93,94). Inhibition of FASN suppresses invasion and migration of HCC cells (95). In contrast to enhanced fatty acid synthesis, certain types of cancer rely on the mitochondrial fatty acid oxidation (FAO) for ATP production (96). Although the mechanism that upregulates FAO in cancer remains unclear, it is proposed that FAO may confer benefits beyond ATP production (96). The FAO contributes to maintenance of redox homeostasis, and cell survival in hematopoietic stem cells and leukemia cells (97). Carnitine palmitoyltransferase (CPT1), the enzyme that catalyzes the initial step of FAO, is implicated in various types of cancer (96,98,99). CPT1 upregulation increases FAO, ATP production and endows resistance to metabolic stress.

7. Metabolic crosstalk

Increased glucose consumption, lactate production, PPP, lipid metabolism, and amino acid synthesis are commonly observed metabolic profile in almost all types of cancer cell. This type of metabolic profiling of tumor cells has been proposed to support their rapid cell growth (100). High rates of glycolysis leading to lactate production (aerobic glycolysis or the Warburg effect) distinguish cancer cells from normal cells (12,13). Glucose is a remarkable fuel for cancer cell, and a precursor for the supply of various metabolic intermediates, which are utilized for lipid, amino acid and nucleotide synthesis. Glutamine serves as another important source of fuel in cancer cells (65). Glutamine enters the mitochondria to replenish the Krebs cycle intermediates (66-69). Glutamine enters the Krebs cycle to produce α -KG, succinate, fumarate and malate. Highly proliferative cancer cells have a high demand for the rapid synthesis of lipids, amino acids and nucleotides (83-87). Tumor cells also divert carbon from glycolysis into the PPP (58), by which cancer cells synthesize macromolecules, such as nucleic acids. In addition, citrate and acetyl-coA are key intermediates for lipid synthesis (88-90). Since these metabolic pathways are interconnected, understanding the mechanism(s) leading to this metabolic switch in cancer cells is of utmost importance.

8. Central role of mitochondria

Mitochondrial metabolism has emerged as a key target for cancer therapy (8,9). Mitochondria are important bioenergetics and biosynthetic organelles, responsible for producing ATP and various intermediates required for macromolecule

synthesis. In addition to participating in energy metabolism, mitochondria participate in calcium homeostasis, production of reactive oxygen species (ROS), regulation of apoptosis and cell signaling pathways (3-6). Cancer cells have been shown to exhibit various degrees of mitochondrial abnormalities, which render mitochondria a suitable target for anti-cancer drugs (7-9). Mutations in mitochondrial DNA- and nuclear DNA-encoded mitochondrial genes have been observed in various types of human cancer (101-103). These mutations range from single nucleotide polymorphisms to severe insertions/deletions and even chain termination. Furthermore, as mitochondria are the primary source of ROS generation, mitochondrial DNA is continuously exposed to oxidative stress and damage. A previous study investigated the contributions of mitochondrial mutations to tumor cell proliferation and metastasis (104). With increasing mutations, mitochondrial respiratory capacity has been shown to decrease progressively (104,105). In addition, defects in the mitochondrial respiratory chain may either promote or inhibit apoptosis (106). Programmed cell death or apoptosis is a complex signaling cascade, which is tightly regulated by proteases, termed caspases. Initiation of apoptosis and ROS production are closely associated with mitochondria (107). Osellame *et al* (107), demonstrated that loss of mitochondrial outer membrane permeability is characteristic of intrinsic apoptosis. In addition, ROS may mediate pro- and anti-apoptotic effects (108). During the last decade, the implication of polyamines in initiation of apoptosis has been the focus of investigations (109,110). Novel interactions between polyamine and mitochondria have recently been summarized in a review by Grancara *et al* (111). There is increasing interest in understanding multiple facets of mitochondrial biology that contribute to cancer. Mitochondria act as a central hub for cell survival, cell metabolism and cell death pathways. Taking into consideration the multifaceted role of mitochondria in tumorigenesis, targeting mitochondria may present an effective approach to treating cancer.

9. Conclusion

Metabolic reprogramming of cancer cells is recognized as one of the hallmarks of cancer. In this review article, the core dysregulated metabolic pathways and enzymes contributing to cancer cell proliferation, differentiation and metastasis, as well as the central role of mitochondria in orchestrating metabolic reprogramming were summarized. The close connection between these metabolic pathways, the role of mitochondria and redox regulation of tumor cells represents a promising strategy to target cancer growth. Thus, targeting these important metabolic enzymes and/or mitochondrial metabolic pathways may offer a valid and novel anti-cancer therapeutic strategy.

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