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Components of Cancer Metabolism and Therapeutic Interventions

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Abstract

All forms of life share a common indispensible need of energy. The requirement of energy is necessary for an organism not only to survive but also to thrive. The metabolic activities in normal cells rely predominately on mitochondrial oxidative phophorylation for energy generation in the form of ATP. On the contrary, cancer cells predominately rely on glycolysis rather than oxidative phosphorylation. It is long believed that an impairment of mitochondrial oxidative phosphorylation is the cause of this glycolytic phenotype observed in cancers. However, studies in cancer metabolism have revealed that mitochondrial function in many cancers is intact. It has also been observed that cancers utilize various forms of metabolism. The various metabolic phenotypes are employed by cancer cells have a common purpose, to balance macromolecular biosynthesis and sufficient ATP production in order to support the rapid proliferation rate characteristic of these aberrant cells. These metabolic pathways are attractive targets for possible therapeutic interventions and currently research is underway to meet this end. More importantly, normal cells have essentially the same metabolic requirements as cancer cells so finding an approach to target these metabolic pathways without incurring detrimental effects on normal tissues remain the challenge.

INTRODUCTION

All cells are completely reliant on the presence of an adequate supply of energy in order to carry out cellular processes like proliferation and macromolecular biosynthesis. This inherent need for a constant supply of energy also applies to cancer cells. Cancer proliferation alone is very costly process in terms of energy requirements due to the several anabolic reactions it encompasses as well as the procurement of the necessary basic components such as; nucleic acid, protein and lipids. Cancer cells have been able to meet

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this need of energy by utilizing metabolic pathways that produce enough ATP and necessary metabolites to not only survive but also proliferate in environments that normal cells would find inhospitable such as hypoxic and acidic conditions.

Metabolic activities of normal cells in regard to energy production rely predominately on the aerobic process of mitochondrial oxidative phosphorylation (OXPHOS), which is efficient and produces more ATP than its anaerobic counterpart glycolysis. Cancer cells exhibit the use of the metabolic oddity of aerobic glycolysis also known as the Warburg effect. This inefficient metabolic pathway consisting of glycolysis in the presence of an aerobic environment was first described by Dr. Otto Warburg (Warburg et al., 1924). Dr. Warburg proposed that the presence of aerobic glycolysis was the result of permanent dysfunction of the mitochondria. This view of has been recently challenged with research showing that the organelle is in fact functional in many cancers (Fantin et al., 2006). In addition, the notion that cancers can subsist on aerobic glycolysis alone is discredited in the face of research showing that glutamine metabolism (glutaminolysis) is essential for some cancers survival (Yuneva et al., 2007). Glutamine can be utilized for the synthesis of protein, nucleic acid, the anti oxidant glutathione, lipids or serve an anaplerotic role in order to provide an energy source (Dang, 2009).

Interestingly, the metabolic phenotypes of cancer cells vary greatly; within a single tumor heterogeneity can be seen from cell to cell. The metabolic heterogeneity observed in cancers is influenced by the surrounding microenvironment. The potential gradients of oxygen, nutrients and pH due to abnormal tumor vasculature all comprise to make up the microenvironment (Cairns et al., 2011).

Currently research is underway in order to distinguish potential cancer cell specific metabolic targets so that therapeutic agents can be developed. The purpose of this article is to review the research on the cancer metabolism components of aerobic glycolysis, glutaminolysis, mitochondrial function and possible therapeutic interventions that can target cancer cell-specific metabolic processes.

AEROBIC GLYCOLYSIS

The metabolic hallmark of most cancer cells is the avid uptake and metabolization of glucose. The preferential utilization of glycolysis by cancer confers many advantages. The first is that by utilizing aerobic glycolysis cancer cells can live in environments of fluctuating oxygen concentration that would prove fatal for cells that relied predominately on oxidative phosphorylation to generate ATP (Pouyssegur et al., 2006). Second is the production of lactate, which is the end product of aerobic glycolysis, which makes the proximate environment acidic, favoring cancer invasion (Swietach et al., 2007) and suppressing anti-cancer immune effectors (Fischer et al., 2007). Third is that cancer cells use the intermediates from the glycolytic pathway for anabolic reactions necessary for rapid proliferation (Gatenby and Gillies, 2004). Forth is that pyruvate and NADPH, the end products of the two main pathways for glucose metabolism (glycolysis and pentose phosphate pathway, PPP, respectively), are used by cancer cells to fight against oxidative stress. Pyruvate has been shown to scavenge hydroperoxides (Nath et al., 1995). NADPH,

one of the major product of PPP has been shown to participate in glutathione peroxidase (GPX) mediated destruction of hydrogenperoxides.

Transcription factors, tumor suppressors and oncogenes regulate glycolysis. Oncogene Ras mutations have been identified in many cancers and drive the metabolic phenotype towards aerobic glycolysis (Hu et al., 2012). Ras activates the mammalian target of rapamycin (mTOR) via the PI3K signaling and mTOR stimulates glycolysis through the induction of hypoxia inducible factors (HIF), specifically isoform HIF1 (Majmundar et al., 2010). A large pool of evidence suggests the role of HIF in the upregulation of biological pathways implicated in cancer progression. HIF1 is an inducible transcription factor that promotes cellular adaptation to hypoxic environments and ultimately facilitates the shift from OXPHOS to the glycolytic phenotype in cancer. HIF1 is regulated by oxygen concentrations which are significantly reduced in cancer cells. Lower oxygen inhibits HIF1 ubiquitination and degradation, therefore prolongs its transcriptional activity. In regard to energy metabolism, HIF1 induces glucose transporter (GLUT) 1 and 3 expression as well as upregulates 9 of 10 glycolytic enzymes (except phosphoglycerate mutase) that function in glycolysis (Levine and Puzio-Kuter, 2010). HIF1 also inhibits the conversion of pyruvate to acetyl-CoA through the activation of pyruvate dehydrogenase kinase 1 (PDK1), resulting in a decrease in mitochondrial OXPHOS. Studies have also shown that upregulation of pyruvate kinase M2 (PKM2) by mTOR is critical for aerobic glycolysis and cancer growth (Sun et al., 2011). PKM2 occupies the last position of the glycolytic pathway and possesses two possible configurations a tetramer (more active) and a dimer (less active). When cellular energy demands are high the tetrameric form of PKM2 is prevalent and glycolysis is carried out to lactate production. When the cell is in a proliferation state the dimeric form of PKM2 is prevalent resulting in the accumulation of phosphometabolites upstream of pyruvate in the glycolytic pathway to serve as precursors for the synthesis of nucleic acids, amino acids and lipids while the production of lactate is avoided (Mazurek et al., 2005). mTOR upregulates PKM2 via HIF1 and Myc (Sun et al., 2011), which is consistent with Myc upregulation of glycolysis. The oncogene Myc, which is commonly overexpressed in human cancers, is a transcription factor that regulates approximately 15% of human genes, including metabolism (glucose, glutamine, protein, and lipid), cell cycle and apoptosis to name a few. Myc upregulates the expression of GLUT and lactate dehydrogenase-A (LDH-A), which directly contributes to the glycolytic pathway. HIF1 binds to the promoter region of *Myc* and enhances its transcription. HIF1 and c-Myc also show cooperation to promote aerobic glycolysis through the induction of hexokinase 2 (HK2) and pyruvate dehydrogenase kinase 1 (PDK1), with the former converting glucose to glucose 6-phosphate (G6P) and the later acting as a negative regulator on the pyruvate dehydrogenase (PDH) (Dang et al., 2008). G6P is continuously produced in hypoxic cancer cells through the activity of HK2, and HK2 is reported to be the facilitator and gatekeeper of malignancy (Mathupala et al., 2006).

Tumor suppressor p53 is one of the most common gene mutations seen in cancers. p53 is a transcription factor that serves as a regulator of various cellular processes including cellular energy metabolism. p53 plays a crucial role in cellular energy metabolism by balancing between OXPHOS and glycolysis (Ma et al., 2007). The combination of the transcription factors p53, c-Myc and HIF1 has been described as the “triad” of transcription factors

responsible for the glycolytic phenotype seen in cancerous cell (Yeung et al., 2008). The action of p53 in normal conditions in regard to cell metabolism is the downregulation of the expression of GLUT 1&4 and HK2, and the upregulation of expression of p53 induced glycolysis and apoptosis regulator TIGAR and synthesis of cytochrome c oxidase 2 (SCO2) and apoptosis inducing factor (AIF) (Wang et al., 2012). Thus, the role of p53 on cellular energy metabolism is to inhibit glycolysis and promote OXPHOS. The enzyme TIGAR inhibits glycolytic activity through the dephosphorylation of fructose-2,6 bisphosphate, which is an important allosteric effector of phosphofructose kinase 1 (PFK1) a key regulatory enzyme of glycolysis. SCO2 promotes the assembly of cytochrome c oxidase complex in the mitochondrial electron transport chain (ETC) complex IV while, AIF is critical for the function of ETC complex I. The defiency of p53 gives way to reduced SCO2 and AIF activity ultimately resulting in mitochondrial OXPHOS impairment (Zhou et al., 2003). p53 also serves the role of a negative regulator of HIF1, p53 inhibits HIF1 through the induction of microRNA-107. The inactivation of p53 permits aerobic glycolysis in various ways including the increased uptake of glucose and activity of HIF1, HK2 and phosphoglycerate mutase (PGM) as well as the decrease of TIGAR, SCO2 and AIF expression. As above mentioned, under hypoxic conditions, mitochondria have developed a more efficient mechanism of respiration by modifying expression of the electron transport chain proteins, rendering cancer cells to respond to hypoxia.

GLUTAMINOLYSIS

Though it is widely accepted that glucose is the predominate energy source for most cancer cells, research has shown it is not the only one (Guppy et al., 2002). The metabolic pathway of glutaminolysis has been identified as an alternative for energy production in certain cancers since high glutamine consumption has been frequently observed (DeBerardinis et al., 2010). Glutamine metabolism has been observed in well known cell lines such as HeLa, where it has been reported that this cell line was in fact glutamine rather than glucose dependent (Reitzer et al., 1979). The process of glutaminolysis begins with its entry into the cell membrane through transporters SLC1A5 or SLC7A, which are members of the soluble carrier family 1 (neutral amino acid transporters) and 7 (cationic amino acid transporters) respectively (Dang., 2009). Once entry into the cell has been achieved, glutamine can then be used as an amino acid for protein synthesis, a nitrogen donor for nucleic acid synthesis, an element of the anti-oxidant glutathione, a precursor (citrate) for the synthesis of lipids or as an energy source through an anaplerotic reaction. The utilization of glutamine as energy source is initiated by its transportation into the mitochondria where it is subsequently catabolized into glutamate and ammonia by the mitochondrial enzyme glutaminase (GLS). Glutamate is then further catabolized by the enzyme glutamate dehydrogenase to α-ketoglutarate, which is then oxidized in the citric acid cycle to produce high energy electrons (NADH & $FADH_2$) and ATP. The citric acid cycle intermediate malate can be shuttled out of the mitochondria into the cytosol where it is oxidized to pyruvate producing large quanities of NADPH that is needed for the anabolic reactions necessary for cell proliferation. Elevation of glutamine consumption in cancer cells is closely related to Myc activation in those respective cell lines. It has been reported that Myc transformed cells become “addicted” to glutamine; this had been surmised through increased expression of

glutamine transporters such as SLC1A5 and catabolic glutamine enzymes (Wise et al., 2008). Myc induction of a B cell model of Burkitt's lymphoma shows significantly increased levels of glutaminase 1 (GLS). Interestingly, the GLS mRNA is unaltered by Myc induction, while GLS is significantly induced. This observation suggested that GLS is being regulated post transcriptionally by Myc. It is then determined that increased expression of GLS is due to the direct repression of miR-23a/b by Myc (Gao et al., 2009). Other studies have shown the effects of Myc on glutaminolysis. Myc transfected human fibroblasts are deprived of glucose and subsequently died but death is not by apoptosis evidenced by the absence of the characteristic nuclear morphology (condensed chromatin). In contrast, Myc transfected human fibroblasts are deprived of glutamine and died by apoptosis as evidenced by the characteristic nuclear morphology (Yuneva et al., 2007). The deprivation of glucose has a lethal effect on cancerous cells (Simons et al., 2009) but it may also harm normal cells; however, the deprivation glutamine has a lethal effect specifically on cells induced by Myc. These data suggest that interfering with glutaminolysis may become a useful therapeutic option when dealing with glutamine dependent cancers.

MITOCHONDRIAL FUNCTION

Dr. Warburg proposed that the presence of aerobic glycolysis was the result of permanent dysfunction of the mitochondria. This view has been challenged by studies that show the organelle is in fact functional in many cancers (Fantin et al., 2006). Some researchers consider the theory that the Warburg effect seen in cancer is due to enhanced glycolysis suppressing OXPHOS rather than an inherent defect in mitochondrial OXPHOS. It has been proposed that the inhibition of glycolysis in cancer cells could ultimately restore mitochondrial OXPHOS function. This proposal has been shown to be valid through the process of LDH-A suppression in cancer cells, which ultimately illustrates that OXPHOS could be enhanced in order to compensate for decreased ATP due to inhibition of glycolysis. It has also been seen that the proliferation and tumorigenicity of the cancer cells is inhibited when LDH-A is suppressed, suggesting that OXPHOS is not sufficient alone to meet the metabolic requirements of cancer (Fantin et al., 2006). These observations suggest that some cancer cells reserve the capacity to utilize OXPHOS in order to produce ATP, which enhanced OXPHOS alone is not sufficient to meet the requirements of cancer growth and that LDH-A is a potentially useful target for cancer therapy. The reverse Warburg effect is a current hypothesis that supports the role of OXPHOS in cancer cells. The reverse Warburg effect proposes that epithelial cancer cells induce aerobic glycolysis in neighboring stromal fibroblasts. These cancer associated fibroblast then undergo myo-fibroblastic differentiation and begin to secrete lactate and pyruvate, which is then taken up by epithelial cancer cells in order to incorporate them into the mitochondrial TCA cycle which would result in high ATP production via OXPHOS (Pavlides et al., 2009). It has been demonstrated through a recent study that lactate and ketones derived from glycolyis when released by hypoxic cancer cells and/or stromal cells can be taken up by oxygenated cancer cell and utilized as an energy source through mitochondrial OXPHOS in order to drive cancer cell growth and metastasis (Bonuccelli et al., 2010). These studies have demonstrated that a metabolic symbiosis exists between epithelial cancer cells and neighboring stromal cells. The existence of the metabolic symbiosis is not excusive to cancerous tissues but this process can be seen in normal tissue

as well. The brain neurons depend on OXPHOS in order to meet their energy requirements in contrast to astrocytes which derive their energy requirements from glycloysis. Astrocytes release lactate, which can then be taken up by neurons and utilized in OXPHOS for energy production, this metabolic cooperation between these two tissues is called the astrocyte-neuron lactate shuttle (Belanger et al., 2011). Mitochondrial defects in aerobic respiration can be present in cancer cells even they may maintain OXPHOS function. The observed increase of glycolysis in certain cancers can be contributed to compromised mitochondrial function (Chandra et al., 2011) including decreased expression of mitochondrial oxidative enzymes and transporters, truncated TCA cycle, decreases in the amount of mitochondria per cell, inhibition of ATP synthase, and elevated sensitivity of mitochondrial DNA to oxidative stress that results from OXPHOS (Moreno-Sanchez et al., 2007).

Cancer is often considered as a genetic disease and mutations in mitochondrial proteins have been linked to cancer development. Succinate dehydrogenase (SDH) of ETC has four subunits: A, B, C and D. Mutations in SDH lead to increased oxygen production further leading to an increased sensitivity to oxidative stress (Slane et al., 2006). In addition, mutations in B,C and D subunits has been linked to familial forms of human cancer (Paraganglioma and Pheochromocytoma) (Astuti et al., 2003). Fumarate hydratase (FH) is a homotetrameric TCA cycle enzyme. A heterozygous FH mutation is correlated with renal cell carcinoma (Tomlinson et al., 2002). Growing evidence show the involvement of FH mutation in bladder (Yeisaukko-Oja et al, 2006) and Leydig Cell tumor (Carvajal-Carmona et al., 2006). Moreover, the mutation of SDH and FH genes are characterized by the activation of HIF1 (Lehtonen et al., 2007), which is mediated by that these mutations lead to inhibition of PHD (Prolyl 4 hydroxylase) which negatively regulated the stability of HIF1.

Mitochondrial dysfunction may result in growth advantage for cancer cell migration and invasion. Rotenone-incubated human breast cancer cells are more aggressive than their parental cells, which is mediated by ROS-induced upregulation of CXCL14 (Pelicano et al., 2009) or HIF1 and vascular endothelial growth factor (Ma et al., 2013). Similar results are also reported in invasive melanoma cells (Comito et al., 2011), in which mitochondrial ROS actually stabilize HIF1 which in turn activates the Met oncogene.

THERAPEUTIC INTERVENTION

The growth and survival of all cells is dependent on metabolic processes such as macromolecular synthesis and ATP production. Proliferating cancer cells have appreciable differences in metabolic requirements in contrast to normal cells. Cancer cells utilize various metabolic pathways such as aerobic glycolysis, glutmainolysis and OX PHOS in order to support the high rate of proliferation characteristic of these aberrant cells. The cancer cells metabolic pathways must be reconfigured in a way that balances macromolecular biosynthesis and sufficient ATP production in order to support the rapidly proliferation rate and overall cell survival. These metabolic pathway reconfigurations provide an attractive target for possible therapeutic interventions (Luo et al., 2009). However, normal cells have essentially the same metabolic requirements as cancer cells so finding an approach to target these metabolic pathways without incurring detrimental effects on normal tissues remains a challenge. Metabolism at the level of the organism as a whole may influence cancer

initiation and progression. Obesity, hyperglycemia and insulin resistance are all associated with an increased risk of developing cancer and all are associated with poor clinical outcomes in patients with cancer (Calle et al., 2004, Jee et al., 2005). Elevated levels of insulin and insulin like growth factor (IGF) have been associated with cancer progression, which implies that insulin resistance could possibly promote cancer at least in the way of activation of signaling pathways that precipitate cell growth (Pollack., 2008). The antidiabetic drug metformin is being investigated for anticancer activities. Retrospective clinical studies have shown a reduction in cancer related mortality in diabetic patients who are taking metformin. This effect appears to be independent of blood glucose levels, due to the fact diabetic patients whose blood glucose is controlled by other means do not acquire the anticancer effect as patients utilizing metformin (Evans et al., 2005). Metformin is a biguanide that acts through the inhibition of mitochondrial complex 1 in the liver to interfere with ATP formation. This interference of energy production causes energy stress, increased AMP activated protein kinase (AMPK) activity, and inhibition of gluconeogenesis, resulting in lower blood glucose levels and decreased insulin secretion due to improved insulin sensitivity (Shaw et al., 2005). Therefore it is debated if metformin benefits patients with cancer through the direct action on the cancer or indirect action by decreasing levels of insulin and insulin like growth factor. AMPK serves as a metabolic checkpoint, which is activated in times of energy stress such as the presence of an increased AMP/ATP ratio and is responsible for shifting the cell into an oxidative metabolic state as well as inhibiting cell proliferation. Cancer cells then must overcome this checkpoint in order to divide under abnormal nutrient conditions, which is achieved through oncogenic mutations like those seen in liver kinase B1 (LKB1) (Shackelford et al., 2009). LKB1 is a kinase that serves a crucial role for AMPK activation, which is frequently deficient in human cancers (Wingo et al., 2009). Metformin acts as an AMPK agonist and is being evaluated to determine if it in fact possesses any inherent anticancer activity.

The application of enzymes that target the unique metabolisms of cancer cells has been utilized in current and proposed cancer therapy. Successful therapeutic therapies illustrate that cancer metabolism is in fact a proven target. The use of the enzyme L-asparaginase to treat acute lymphoblastic leukemia (ALL) has been proven efficacious and as a result it is a cornerstone of current ALL therapy protocols. The rationale for the use of L-asparaginase is that lymphoblastic leukemia cells are asparagine as well as glutamine auxotrophs and as a result depend on extracellular sources of these amino acids. L-asparaginase deaminates asparagine to aspartic acid, essentially depleting serum asparagine. The depletion of serum asparagine leads to the reduction of RNA, DNA and protein synthesis and ultimately the death of leukemic cells (Mueller et al., 1998). Currently there are three forms of asparaginase that are derived from two bacterial sources. Native asparaginase and pegylated asparaginase are both derived from *Escherichia coli*, while crisantaspase is derived from *Erwina chrysanthemi* (Pieters et al., 2011). All three forms of asparaginase share the same mechanism of action but differ on their own unique pharmacokinetic properties subsequently they are not interchangeable at the same dosage and frequency of administration (Asselin et al., 1993). Bacterial L-asparaginase used clinically has preferential selectivity for asparagine over glutamine, which is a structurally related amino acid. However the enzyme retains some ability to degrade glutamine (Derst et al., 2000) and

this may play a role in the dose dependent coagulopathy caused by the unequal synthesis of pro- and anticoagulants (Ollenschlager et al., 1988). Glutamine is a crucial nutrient for many cancers and it depletion may contribute to the effectiveness of asparaginase on ALL. The therapeutic success of L-asparaginase has lead to approach of identifying other autotrophies of cancer cells. This approach has yielded the observation that several types of cancer cells possess low level of the enzyme arginosuccinate synthetase, which is responsible for the endogenous synthesis of arginine. Cancer sensitivity to depletion of arginine was suggested in earlier experiments (Bach et al., 1965). Arginine deiminase conjugated with polyethylene glycol is an agent that diminishes extracellular levels of arginine and is currently in clinical trials for its potential therapeutic application in various cancers (Ni et al., 2008). Phase I/II trials have shown that this agent can be safely administered as well as positive responses in melanoma (Ni et al., 2008) and hepatocellular carcinoma (Yang et al. 2010).

Central cancer metabolism pathways can be safely targeted. This is validated when considering dichloroacetate (DCA), which is a therapeutic agent used to treat rare inborn errors of mitochondrial metabolism, specifically congenital lactic acidosis. A controlled clinical trial in a pediatric population showed DCA to be well tolerating by patients as well as to decrease postprandial circulating lactate (Stacpoole et al., 2006). The target of DCA is pyruvate dehydrogenase kinase (PDK), which exhibits increased expression in many cancers as a result of the increased activation of HIF. PDK serves as an inhibitor of pyruvate dehydrogenase complex (PDH) (Kim et al., 2006). PDH functions to catalyze the oxidative decarboxylation of pyruvate to acetyl-CoA, thus allowing the entrance of pyruvate into the TCA cycle and diverting it away from lactate formation. Therefore DCA mediated inhibition of PDK results in an increase of oxidative mitochondrial metabolism as well as decreased lactate production. A recent study involving multiple myeloma shows that DCA through the inhibition of aerobic glycolysis and the promotion of oxidation of pyruvate induced growth inhibition of the cancer (Sanchez et al., 2013).

NAD^+ and NADH are important cofactors for metabolic oxidation-reduction reactions though the amounts of these molecules are limited in the cell. These molecules act as substrates for the enzymes NAD-dependent deacetylase sirtuins and poly(ADP-ribose) polymerases that are involved with processes related to cancer such as DNA repair, inflammation and protein acetylation (Garten et al., 2009). In contrast to oxidation-reduction reactions, the former reactions consume NAD^+ and deplete the limited cellular supply of this necessary cofactor. Nicotinamide phosphoribosyltransferase (NAMPT) is the enzyme that is involved in the regeneration of the NAD^+ from nicotinamide and phosphoribosyl pyrophosphate. NAMPT inhibitor FK866 was identified through a chemical screen with the purpose of identifying cytotoxic compounds. FK866 inhibits NAMPT and depletes the NAD^+ cellular supply, indicating that FK866 could potentially be used against cancer cells that rely on nicotinamide for synthesis of NAD^+ (Hasmann et al., 2003). FK866 induces delayed tumor growth and an enhancement of tumor radiosensitivity accompanied by dose dependent decreases in NAD levels, energy status and pH (Muruganandham et al., 2005). However, NAMPT inhibition has been shown to be toxic to lymphocytes, which suggest NAMPT inhibitors use may be limited by immunosuppression (Bruzzone et al., 2009).

Cancer cells often encounter higher levels of oxidative stress than normal cells and these cells could be particularly sensitive to oxidative stress and ROS-induced apoptosis, which provides an attractive approach for therapy. Mitochondrially targeted redox cycler-doxorubicin, which serves as a source of exogenous ROS production, has been shown effectiveness in killing cancer cells (Malhi et al., 2012). NV-128, a novel isoflavone derivative, can generate mitochondrial superoxide and hydrogen peroxide, killing chemoresistant human ovarian cancer cells (Alvero et al., 2011). Similar strategies have been tested in clinic. Menadione, which undergoes redox cycles on the respiratory chain, has been shown to induce clinical responses in patients with advanced hepatocellular carcinoma (Sarin et al., 2006). β-lapachone, another ROS-producing agent through redox cycling, is currently in clinical trials as monotherapy or in combination with gemcitabine in patients for pancreatic and head and neck cancer (Bey et al., 2007).

CONCLUSION

This review article summarizes several important abnormal metabolic behaviors of cancer cells and how to target these metabolic changes for chemotherapy. The major and also successful strategy at the current stage is to reverse these metabolic changes by using agonists/antagonists to the key metabolic enzymes. With the clinical success of this strategy, targeting cancer metabolism will eventually lead to the generation of a new class of drugs.

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Highlights

- Aerobic glycolysis in cancer cells is regulated by a network of oncogenes and tumor suppressor genes.
- Glutaminolysis is another hallmark of cancer metabolism and it can serve as a unique target for cancer therapy.
- Cancer cells can be either normal or have defects in mitochondrial metabolism. It will be an interesting approach to selectively target each type of mitochondria for thermotherapy.
- Since mitochondrion is the major source of intracellular ROS, boosting mitochondrial ROS production in cancer cells can be an attractive therapeutic approach.