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Review

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 that 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 remains the challenge.

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1. 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 a 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 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

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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, and 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.

2. 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 hydrogen peroxides.

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 that 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, and 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 deficiency 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 mentioned above, 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.

3. Glutaminolysis

Although 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 and Cheng, 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

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