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Review

Dysregulation of glucose transport, glycolysis, TCA cycle and glutaminolysis by oncogenes and tumor suppressors in cancer cells

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ABSTRACT

A common set of functional characteristics of cancer cells is that cancer cells consume a large amount of glucose, maintain high rate of glycolysis and convert a majority of glucose into lactic acid even in the presence of oxygen compared to that of normal cells (Warburg's Effects). In addition, cancer cells exhibit substantial alterations in several energy metabolism pathways including glucose transport, tricarboxylic acid (TCA) cycle, glutaminolysis, mitochondrial respiratory chain oxidative phosphorylation and pentose phosphate pathway (PPP). In the present work, we focused on reviewing the current knowledge about the dysregulation of the proteins/enzymes involved in the key regulatory steps of glucose transport, glycolysis, TCA cycle and glutaminolysis by several oncogenes including c-Myc and hypoxia inducible factor-1 (HIF-1) and tumor suppressor, p53, in cancer cells. The dysregulation of glucose transport and energy metabolism pathways by oncogenes and lost functions of the tumor suppressors have been implicated as important biomarkers for cancer detection and as valuable targets for the development of new anticancer therapies.

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1. Introduction

Cancer cells exhibit a common set of functional characteristics, i.e. they consume a larger amount of glucose, maintain a much higher rate of glycolysis and convert a majority of glucose into lactic acid even in the presence of oxygen compared to that of normal cells. This phenomenon was first described over 70 years ago [1,2] and has been known as the Warburg's Effect (aerobic glycolysis) [3]. The tumor cells preferentially use glycolysis over mitochondrial oxidative phosphorylation for glucose-dependent ATP production. This deviant energetic metabolism is a potential hallmark of cancer cells and has been thought to be the root of tumor formation and growth [4]. While the mechanisms underlying the Warburg's Effects have not been completely understood, a number of oncogenes including C-Myc and hypoxia inducible factors-1 (HIF-1) and tumor suppressors such as p53 have been known to be involved in the regulation of energy metabolism (for review see [5,6]). The notable factors crucial for cancer metabolic phenotype are oncogenic mutations that alter growth factor signaling through the Phosphoinositide 3-kinase (PI3K)/Akt (Protein Kinase B, PKB)/the mammalian target of rapamycin (mTOR) pathway [7]. Activation of this pathway enhances metabolic activities of glycolysis by two major events. First, the synthesis of the sugar transporter GLUT-1 is induced to facilitate glucose uptake by the cells [6,8,9]. Second, the activity of transcription complex HIF-1α is increased, which in cooperation with transcription factor c-Myc enhances the synthesis of the majority of glycolytic enzymes [10]. The distinct phenotype of high glucose uptake in cancer cells has important clinical implications in that it can be documented by positron emission tomography (PET) scanning of human cancers with radiolabeled 2-deoxyglucose and 18F-fluorodeoxy-glucose [11,12].

Based on Warburg's hypothesis, glycolysis is predominately used in cancer cells because of a dysregulation of mitochondrial oxidative phosphorylation. However, not all cancers are PET-positive, and not all models of neoplastic transformation are associated with increased aerobic glycolysis. While hypoxic cells exhibit a shift toward glycolytic metabolism [13], a functional mitochondrial respiratory chain and a glutamine-derived carbon are required for proliferation of most transformed cells [14]. It has been known that most cancer cells do not have defects in mitochondrial metabolism [2], except for rare mutations in succinate dehydrogenase (SDH) or fumarate hydratase (FH), both are enzymes of the tricarboxylic acid (TCA) cycle [6,15,16]. The oncogene c-Myc is known to be involved not only in regulation of glycolysis but also stimulates mitochondrial biogenesis [17] and glutamine catabolism [6,18,19]. Furthermore, a proteomic study of breast cancer brain metastases detected increases in expression of enzymes/proteins involved in glycolysis, TCA cycle, oxidative phosphorylation and pentose phosphate pathways (PPP) [20]. Consistent with this, it has been observed that metabolic changes accompanying transformation and acquisition of metastatic potential in a syngeneic mouse mammary tumor model [21] and in human triple negative breast cancer cell lines MCF-10F series [22] included changes not only in the key metabolites in glycolysis but also in TCA cycle, PPP, and fatty acid/nucleotide biosynthesis. These observations indicate the need of rethinking the prevailing models of cancer metabolism, particularly if these alterations are exploited for therapeutic purposes [6,11].

Oncogenes and tumor suppressors have been linked to the regulation of glucose and energy metabolism, thereby connecting genetic alterations in cancers to their glucose metabolic phenotype [23,24]. A number of the metabolic changes can be attributed to the activation and/or malfunction of oncogenes, and/or loss of tumor suppressors. In this work, we focused on reviewing the current knowledge about the dysregulation of glucose transport, glycolysis, TCA cycle and glutaminolysis by tumor suppressor p53 and oncogenes, c-Myc and HIF-1α, in cancer cells, and then pointed out the potential implications of these biomarkers/targets for cancer detection and for the development of new anticancer therapies.

2. p53, C-Myc and HIF-1 involved in the regulation of glucose transport, glycolysis, TCA cycle, and glutaminolysis

2.1. p53

p53, a well studied tumor suppressor, plays critical roles in the control of a number of cellular processes including apoptosis, cell cycle arrest, genomic stability, and angiogenesis. In its anti-cancer role, p53 works through several mechanisms. It can initiate apoptosis, if DNA damage proves to be irreparable and it can induce growth arrest by holding the cell cycle at the G1/S regulation point on DNA damage recognition [25,26]. p53 mainly exerts its tumor suppression function through the transcriptional regulation of its target genes. Upon its activation induced by oxidative stress, p53 binds to DNA and induces the expression of several different sets of genes including those involved in cell cycle, apoptosis, DNA repair and oxidative stress response [25]. Notably, activation of the expression of the cyclin-dependent kinase inhibitor $p21^{WAF1/CIP1}$ by p53 plays an important role in induction of G1 cell cycle arrest [27,28]. Another important function of p53 is its involvement in the regulation of intracellular reactive oxygen species (ROS) levels, playing an important role in determining the death or survival of cells [29]. p53 can activate numerous genes that results in increased generation of ROS, which contribute to apoptosis [27]. It also functions in a feedback loop in which ROS can signal to further activation of p53 [30]. On the other hand, p53 can induce the expression of proteins that function to lower ROS levels and this antioxidant function of p53 is important in preventing DNA damage and tumor development under low stress conditions [31]. Recent studies have revealed a number of new functions of p53 in the regulation of glucose metabolism and energy metabolism pathways including glucose transport [32], glycolysis [33], TCA cycle [34], glutaminolysis [35,36], mitochondrial respiratory chain/oxidative phosphorylation [37] and PPP [38,39], which will be described below.

2.2. c-Myc

The proto-oncogene c-Myc encodes a transcription factor involved in many cellular processes, including proliferation, cell cycle progression, cell growth, metabolism, angiogenesis, differentiation, cell adhesion, and mobility primarily through transcriptional regulation of

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