Pyruvate Dehydrogenase Kinase as a Potential Therapeutic Target for Malignant Gliomas

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Metabolic aberrations in the form of altered flux through key metabolic pathways are the major hallmarks of several life-threatening malignancies including malignant gliomas. These adaptations play an important role in the enhancement of the survival and proliferation of gliomas at the expense of the surrounding normal/healthy tissues. Recent studies in the field of neurooncology have directly targeted the altered metabolic pathways of malignant tumor cells for the development of anti-cancer drugs. Aerobic glycolysis due to elevated production of lactate from pyruvate regardless of oxygen availability is a common metabolic alteration in most malignancies. Aerobic glycolysis offers survival advantages in addition to generating substrates such as fatty acids, amino acids and nucleotides required for the rapid proliferation of cells. This review outlines the role of pyruvate dehydrogenase kinase (PDK) in gliomas as an inhibitor of pyruvate dehydrogenase that catalyzes the oxidative decarboxylation of pyruvate. An in-depth investigation on the key metabolic enzyme PDK may provide a novel therapeutic approach for the treatment of malignant gliomas.

Key Words: Pyruvate dehydrogenase kinase; Glioma; Gliomagenesis; Dichloroacetate; Hypoxia-inducible factor.

INTRODUCTION

Pyruvate dehydrogenase kinase (PDK) participates in the regulation of the pyruvate dehydrogenase (PDH) complex (PDC), in which PDH is the first component. PDK is a kinase enzyme that acts to inactivate the enzyme PDH by phosphorylating it using adenosine triphosphate (ATP). Four isomeric forms of PDK, namely PDK1-4, exist having tissue specific expression, different activities, and dissimilar phosphorylation rates (see [1] for comprehensive review). PDC, which acts as one of the major enzymes responsible for the regulation of glucose metabolism, is a nuclear-encoded mitochondrial multienzyme complex that catalyzes oxidative decarboxylation of pyruvate to form acetyl-coenzyme A (CoA) and thereby provides the primary link between glycolysis and the tricarboxylic acid (TCA) cycle [2]. A phosphorylation/dephosphorylation cycle regulates the enzymatic activity of PDH, and phosphorylation results in the inactivation of PDH. PDC is composed of three catalytic components namely, PDH (E1), dihydrolipoamide transacetylase (E2) and dihydrolipoamide dehydrogenase (E3). These components are organized into large multimeric complexes together with the structural subunit E3 binding protein. The basic core of the E1 PDH component is a heterotetramer of two alpha and two beta subunits (α2β2), and it catalyzes the first step of pyruvate decarboxylation. PDKs inhibit PDC by catalyzing the phosphorylation of serine residues in the E1 alpha subunit. PDH is one of the most important and pivotal dehydrogenases having control over mitochondrial metabolic pathways and catalyzes the irreversible decarboxylation of pyruvate to acetyl-CoA, CO2 and nicotinamide adenine dinucleotide (reduced form) (NADH). Because PDH controls the entry of carbon into the TCA cycle, regulation of PDH activity governs the entry of carbons derived from carbohydrates into the mitochondria. The reaction has important roles not only in the regulation of mitochondrial energy-producing pathways (TCA and oxidative phosphorylation (OXPHOS)), but also in the generation of biosynthetic intermediates, such as citrate. Glucose is the major source of carbon for mammalian cells, including cancerous cells like gliomas. Glucose is metabolized to generate ATP, through cytosolic glycolysis and oxygen-dependent mitochondrial metabolism, in which most of the reducing po-
Potential is the outcome of the TCA cycle. The entry of glucose into the TCA cycle is controlled by PDH. Thus, the proper functioning of mitochondrial metabolic pathways can only be achieved through the continuous real-time control of PDH. PDK downregulates the activity of PDH and decreases the oxidation of pyruvate in mitochondria and increases the conversion of pyruvate to lactate in the cytosol. Because these regulatory processes in numerous pathological conditions are extensively altered, these alterations may reflect targets for therapeutic interference.

Malignant gliomas are the most frequent primary brain tumors that arise from the supportive non-neuronal cells of the brain, called glial cells [3-5]. Malignant gliomas contain multipotent tumor stem cells having potential to be transformed into variants of normal neural progenitor cells that are responsible for populating and repopulating the tumors [6,7]. Around 30 percent of all brain and central nervous system tumors and 80 percent of all malignant brain tumors are gliomas [8]. In contrast to neurons, glial cells have the potency to divide and multiply, and failure due to any reason in the controlling system of this potency results in the formation of a glioma. Malignant gliomas are among the most fatal human cancers [9,10]. Gliomas are characterized by their infiltrating nature, especially into the surrounding normal brain tissue. Similar to other human cancers, the formation and progression of diffuse gliomas is accompanied by the overexpression of growth factors like platelet-derived growth factor, epidermal growth factor receptor, basic fibroblast growth factor, transforming growth factor-alpha, and insulin-like growth factor-1 causing an autocrine growth-promoting loop, loss of cell cycle control, activation of oncogenes, inactivation of tumor suppressor genes, dysregulation of apoptosis and instability of the genome. The histological presence of microvascular proliferation is also an important identifying feature of high grade malignant gliomas. Malignant gliomas, primarily glioblastomas, contain angiogenic molecules like vascular endothelial growth factor (VEGF) suggesting an “angiogenic switch” for the progression to malignant gliomas [4,11]. Physiologic response to hypoxia causes the occurrence of tumor angiogenesis through the increased transcription of the VEGF gene by the hypoxia-inducible factor (HIF) family of transcription factors [12-14]. Their highly infiltrative nature is one of the major challenges that prevents surgical resections and complicates the effective delivery of several therapies. The augmentation of the tumor in histological grade creates additional features of malignancy: Gliomas are named on the basis of the cell type, with which they share histological characteristics. They are named as ependymomas, astrocytomas (glioblastoma multiforme), oligodendrogiomas and mixed gliomas (e.g., oligoastrocytomas) on the basis of their resemblance with ependymal cells, astrocytes, oligodendrocytes and mixed glial cells, respectively (Fig. 1). Malignant gliomas include glioblastoma [World Health Organization (WHO) grade IV], anaplastic astrocytomas (WHO grade III), mixed anaplastic oligoastrocytomas (WHO grade III), and anaplastic oligodendrogliomas (WHO grade III).

DYSREGULATED METABOLISM AS A HALLMARK OF GLIOMAGENESIS

Growing evidence reveals that all cancers regardless of tissue or cellular origin are a disease of impaired cellular energy metabolism [15]. In addition to the previously well recognized hallmarks of cancers [16-19], aerobic glycolysis or the Warburg effect is also a robust metabolic feature of most tumors [20-24]. Recent studies on gliomas in experimental models show the dependence of glioma cells on glycolysis as the primary source of energy [25]. Upregulated glycolysis has been established as a defining feature of primary and metstatic cancers that results in increased glucose consumption [23]. Malignant gliomas display high rates of glycolysis and lactate production, even in the presence of adequate oxygen, a phenomenon well known as aerobic glycolysis or the Warburg effect. On the other hand, tumor hypoxia results in constitutive upregulation of glycolysis and acidosis, contributing to the tumor resistance to therapeutic agents [23,26]. The progression of gliomagenesis often occurs in a hypoxic microenvironment that compels the use of anaerobic glycolysis as the primary energy source [23]. Hypoxia stabilizes HIF, a transcription factor, which increases the biological aggressiveness of tumors, promoting glycolysis, cellular proliferation, and...