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Restoration of mitochondria function as a target for cancer therapy

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Defective oxidative phosphorylation has a crucial role in the attenuation of mitochondrial function, which confers therapy resistance in cancer. Various factors, including endogenous heat shock proteins (HSPs) and exogenous agents such as dichloroacetate, restore respiratory and other physiological functions of mitochondria in cancer cells. Functional mitochondria might ultimately lead to the restoration of apoptosis in cancer cells that are refractory to current anticancer agents. Here, we summarize the key reasons contributing to mitochondria dysfunction in cancer cells and whether and/or how restoration of mitochondrial function could be exploited for cancer therapeutics.

Introduction

Q2 Normal cellular growth and development require optimal function of all the regulatory physiological pathways, and any defect in any one or more of these pathways can have adverse effects on the entire cellular homeostasis. Growth and developmental signaling circuits are tightly regulated in normal cells, which tolerate, resist or die in response to external or internal stimuli [1]. Deregulation of these signaling pathways has been implicated in many human diseases, including diabetes, neurodegenerative disorders, developmental defects, and cancer [2]. Defects in pathways regulating cell growth and apoptosis contribute to the carcinogenesis process and are involved in the metastatic progression of tumors [3]. Advanced and metastatic malignancies are characterized by higher rates of cell proliferation and attenuated apoptosis or other cell death signaling [2,4]. Therefore, current strategies in cancer management target these two processes to retard tumor growth and metastatic progression, resulting in a reduction of disease-related burden in patients.

Defects in apoptosis are among the primary cellular malfunctions observed in tumor initiation, growth, and metastatic progression [3]. Current conventional therapies are designed to induce cell death in cancer with minimal toxic effects to the surrounding normal tissues [5,6]. Mitochondrial apoptosis is a complex process that is tightly regulated at multiple steps. It involves the release of cytochrome C from mitochondria and subsequent formation of the apoptosome and caspase activation followed by cell death induction [7]. Cancer cells exhibit strong metabolic 'advantageous faults', which include increased fatty acid synthesis, boosted glutamine metabolism, and dependence on aerobic glycolysis for energy needs [3,8,9] (Fig. 1). These properties of cancer cells are normally referred to as the 'Warburg effect' [10–13]. All these metabolic adaptations contribute to the development of resistance to current cancer treatments, and subsequent apoptosis evasion in cancer cells [14,15]. Therefore, exploiting and targeting such metabolic faults could be an attractive strategy in cancer control and management [9,16]. The physiological status of mitochondria is directly correlated with steady-state oxidative phosphorylation (OXPHOS) and has the potential to induce apoptosis in response to apoptotic stimulus. Defects in normal mitochondria function have strongly been linked to attenuation of apoptosis, and hence, increased cancer growth and progression (Fig. 1) [17–19]. Studies suggest that OXPHOS defects in cancer are an important factor in apoptosis evasion [18]. Thus, changes in mitochondrial DNA (mtDNA), which encodes various proteins, including OXPHOS complex components, are linked to cancer [12,13,17].

Recently, there has been renewed interest in targeting and restoring mitochondrial steady state as an attractive strategy for cancer control and management [20]. Metabolic inhibitors,

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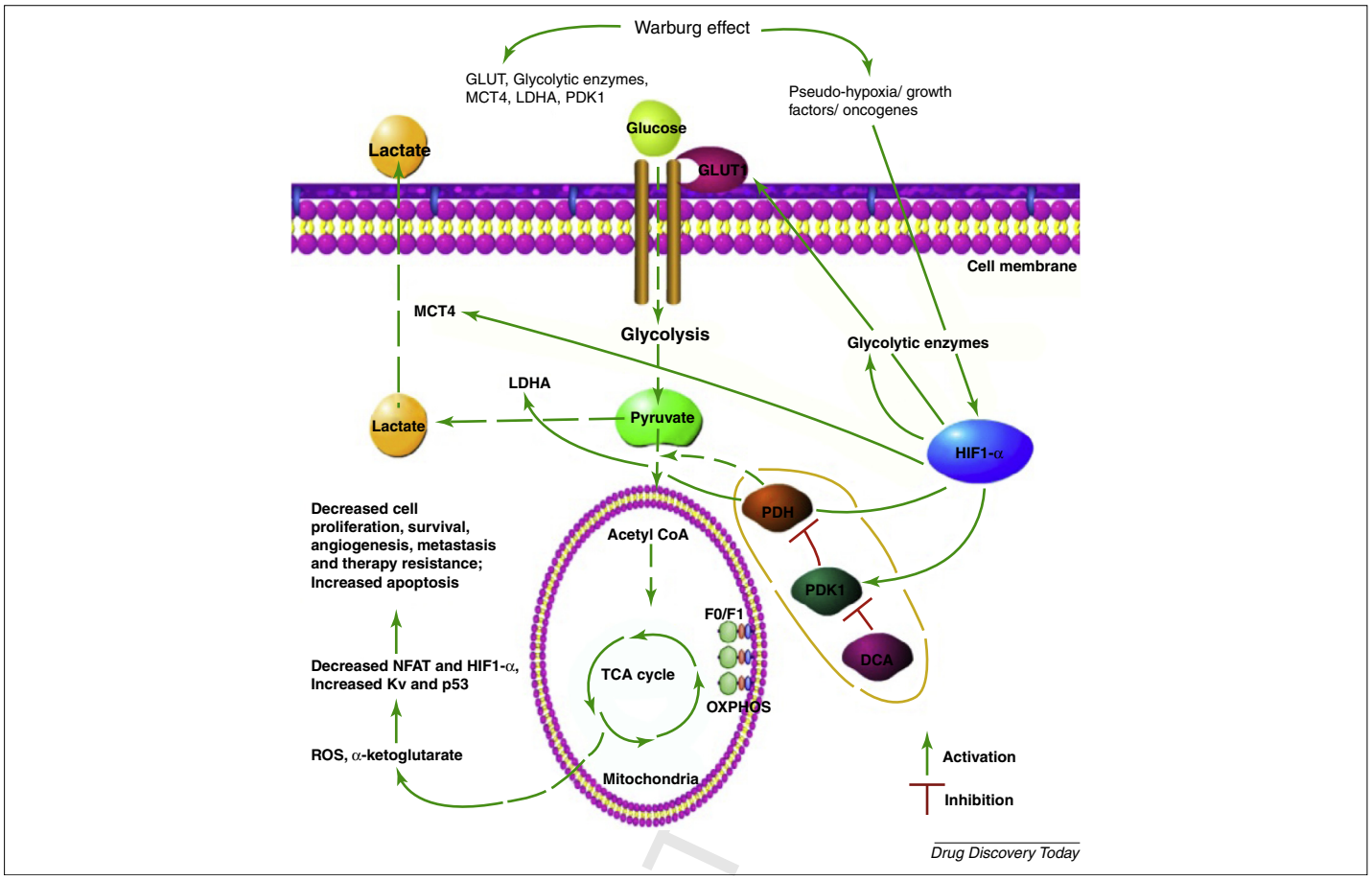

FIGURE 1

The Warburg effect in cancer cells. Aerobic glycolysis leads to pseudo hypoxic signals that upregulate hypoxia-inducible factor-1alpha (HIF-1α), which in turn regulates the expression of genes related to glucose metabolism. HIF-1α is induced by several factors, including hypoxia, growth factors, and oncogenes. HIF-1α induces the glucose transporter GLUT1, which results in an increase demand for glucose by cancer cells. It also enhances glycolysis via upregulation of glycolytic enzymes. HIF-1α-mediated upregulation of pyruvate dehydrogenase kinase (PDK) inhibits pyruvate conversion into acetyl-co-enzyme A (CoA) via suppression of pyruvate dehydrogenase (PDH). Lactate dehydrogenase A (LDHA) induction by HIF-1α leads to lactate production from pyruvate, which is transported to the external cell environment by monocarboxylate transporter-4 (MTC4), another target of HIF-1α. The anticancer agent dichloroacetate (DCA) suppresses PDK and restores PDH activity, leading to pyruvate entry into mitochondria to reactivate the tricarboxylic acid cycle (TCA) and oxidative phosphorylation (OXPHOS). Subsequently, activation of OXPHOS produced reactive oxygen species (ROS) and α-ketoglutarate, which ultimately lead to the induction of apoptosis, suppression of cancer cell growth and survival, inhibition of angiogenesis and metastasis, and overcoming of tumor resistance.

including 2-deoxy-D-glucose (2DG), dichloroacetate (DCA), hexokinase inhibitors, and lactate dehydrogenase (LDH) inhibitors, have been used to specifically block aerobic glycolytic pathway and restore steady-state OXPHOS, and have been shown to be effective against various cancers *in vitro* and *in vivo* (Fig. 1) [16]. In this regard, DCA has shown positive outcomes by inhibiting growth and proliferation of various cancers *in vitro* and *in vivo* by inducing cell cycle arrest and apoptosis [21,22]. DCA is a small molecule of 150 Da and can penetrate all major tissue types, including brain tissue [23]. Thus, targeting metabolic differences between normal and cancer cells is a rational approach in cancer control and management. Here, we discuss key metabolic alterations and their impact on cancer control, and whether restoration of mitochondrial function by small molecules such as DCA could be a viable approach for cancer management and control.

Metabolic differences between normal and cancer cells

Cancer cells differ from normal cells in various key metabolic aspects and are more dependent on aerobic glycolysis, glutaminolysis, and fatty acid synthesis for cellular proliferation, survival, and growth [10,24]. To meet their energy needs, normal cells oxidize glucose via the tricarboxylic acid cycle (TCA) in mitochondria to generate 30 ATPs per glucose molecule. By contrast, cancer cells rely heavily on glycolysis to generate two ATPs per glucose molecule in the cytoplasm. Hence, cancer cells upregulate glucose transporters to increase glucose uptake into the cell and meet their energy needs [25–27]. Otto Warburg was the first to observe these effects and postulate that respiration dysfunction in cancer cells prevents glucose oxidation via the TCA in mitochondria [10]. In addition, increased glycolysis also provides metabolites for gluconeogenesis, lipid metabolism, and the pentose phosphate pathway to generate NADPH and macromolecules for anabolic reactions [24,28]. Such bioenergetic differences in the metabolism of cancer cells versus normal cells provide a potential avenue for the development of cancer therapeutics.

Most cancers originate from hypoxic niches where glucose oxidation is hampered because of a lack of oxygen, and glycolysis remains the sole energy-generating mechanism [29,30]. Hypoxia

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