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Review

The role of mitochondrial electron transport in tumorigenesis and metastasis☆

An S. Tan, James W. Baty, Michael V. Berridge *

Malaghan Institute of Medical Research, PO Box 7060, Wellington 6242, New Zealand

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ABSTRACT

Background: Tumor formation and spread via the circulatory and lymphatic drainage systems is associated with metabolic reprogramming that often includes increased glycolytic metabolism relative to mitochondrial energy production. However, cells within a tumor are not identical due to genetic change, clonal evolution and layers of epigenetic reprogramming. In addition, cell hierarchy impinges on metabolic status while tumor cell phenotype and metabolic status will be influenced by the local microenvironment including stromal cells, developing blood and lymphatic vessels and innate and adaptive immune cells. Mitochondrial mutations and changes in mitochondrial electron transport contribute to metabolic remodeling in cancer in ways that are poorly understood.

Scope of Review: This review concerns the role of mitochondria, mitochondrial mutations and mitochondrial electron transport function in tumorigenesis and metastasis.

Major Conclusions: It is concluded that mitochondrial electron transport is required for tumor initiation, growth and metastasis. Nevertheless, defects in mitochondrial electron transport that compromise mitochondrial energy metabolism can contribute to tumor formation and spread. These apparently contradictory phenomena can be reconciled by cells in individual tumors in a particular environment adapting dynamically to optimally balance mitochondrial genome changes and bioenergetic status.

General Significance: Tumors are complex evolving biological systems characterized by genetic and adaptive epigenetic changes. Understanding the complexity of these changes in terms of bioenergetics and metabolic changes will permit the development of better combination anticancer therapies. This article is part of a Special Issue entitled Frontiers of Mitochondrial Research.

1. Introduction

Tumor formation and progression to metastasis is associated with metabolic remodeling that is contributed by both genetic and epigenetic processes. Genetic changes include both nuclear and mitochondrial mutations while epigenetic changes are driven by the environment in which the tumor develops, and by definition occur independently of, but often in concert with genetic alteration. Together, these reprogramming events effectively rebalance tumor bioenergetics (that branch of metabolism concerned with ATP production) in favor of glycolytic energy metabolism over mitochondrial energy production, changes that are associated with a diverse spectrum of metabolic adjustments commensurate with tissue of origin and residence, increased cell proliferation and self-renewal, and poorly differentiated cell function. At the level of individual tumor cells, cells are not identical due to genetic change, clonal evolution and extinction and layers of epigenetic modification. Thus, cell hierarchy impinges metabolic status in a complex and dynamic manner that is influenced by the local microenvironment including stromal cells, developing blood and lymphatic vessels as well as cells of the innate and adaptive immune system. Mitochondrial mutations that alter mitochondrial electron transport function contribute to metabolic remodeling in ways that are poorly understood, but these mutations are not considered to drive tumorigenesis in the same way that oncogenes complement tumor suppressors to initiate tumor formation. This review primarily concerns the role of mitochondria, mitochondrial mutations and mitochondrial electron transport function in tumor development and metastasis.

2. Cancer as a metabolic disease

The view that cancer is basically a metabolic disease was developed in the early decades of the 20th century during which time this view of tumorigenesis was promoted primarily by Otto Warburg [1–4]. The emergence of molecular biology in the following decades, and the subsequent discovery of the genetic origins of cancer muted this classical biochemical explanation of cancer, not before some robust debate that continues today [5]. Nevertheless, the last decade has seen

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* Corresponding author. Tel.: +64 4 499 6914.
E-mail address: mberridge@malaghan.org.nz (M.V. Berridge).

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a renaissance of the view that cancer is a metabolic disease, although the concept promoted stridently by Warburg that mitochondrial damage is the cause of cancer is no longer literally tenable: rather tumor-specific reprogramming of cellular metabolism by oncogenes, tumor suppressors and other metabolic regulators better explain the etiology of cancer [2,6]. In addition, epigenetic changes and metabolic flexibility [2,7–11] contribute to an emerging 21st century consensus of dynamic complex metabolic remodeling in cancer. Similar considerations apply as in non-tumor situations where stem cell homeostasis, committed progenitor cell expansion and stem cell differentiation all involve metabolic reprogramming and redirection of bioenergetic function [6,12,13] that includes metabolic plasticity, transcriptional remodeling and higher level epigenetic changes [14]. Mutations have been reported in several nuclear-encoded mitochondrial enzymes involved in metabolism including fumarate hydratase [15,16], succinate dehydrogenase (SDH) A-D [17] and isocitrate dehydrogenase (IDH) 2 [18,19], while cytosolic phosphoglycerate dehydrogenase (PHGDH) [20,21] and IDH1 [18,19] are also directly involved. A simplified map that locates most of these metabolic enzymes is shown in Fig. 1 together with other metabolic and bioenergetic points of interest mentioned in this review. Many other classical oncogenes and tumor suppressors are indirectly involved in controlling metabolism through key regulatory nodes including mTOR and PI3K/AKT [22]. In addition, MYC, mutant RAS and RAF, PDK and its phosphorylation regulators, PDK1 and PDP2 [23], hexokinase (HK) II relocation to mitochondria [24] and the pyruvate kinase (PK) splice variant, PKM2 [25–27] are all involved in varying degrees in this reprogramming, some more related to cell proliferation than to cancer *per se*.

Recently, the sirtuins, a family of NAD^+ deacetylases and ADP ribosyltransferases, have emerged as key players in regulating metabolic adaptation and genomic stability in cancer [28,29]. Although several studies support a role for SIRT1 as a tumor suppressor through mechanisms that include MYC deacetylation [30], tumor-promoting roles have also been reported for the sirtuins depending on tumor type and signaling pathways involved. For example, SIRT6 has been shown to control glucose homeostasis through histone H3K9 deacetylation via HIF-1α [31] and to suppress aerobic glycolysis [29] while SIRT2 prevents chromosomal instability [32] and mitochondrial SIRT4 is involved in the DNA damage response (DDR) through anapleurotic blockade of glutamine catabolism [33]. Additionally, SIRT7 has recently been

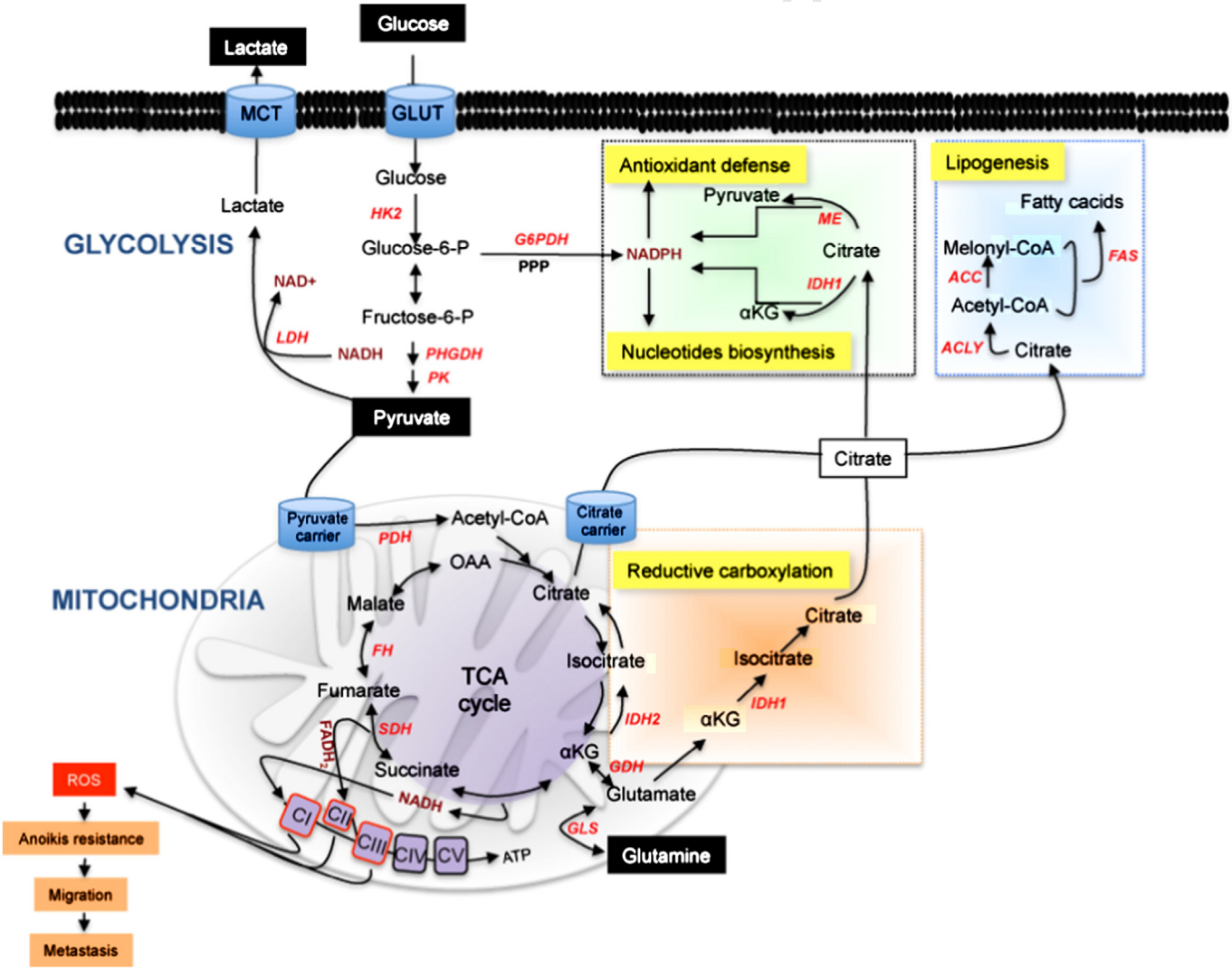

Fig. 1. Major metabolic and bioenergetic pathways involved in tumor cell reprogramming. Abbreviations used: HK2, hexokinase 2; LDH, lactate dehydrogenase; PHGDH, phosphoglycerate dehydrogenase; PK, pyruvate kinase; GAPDH, glucose-6-phosphate dehydrogenase; ME, malic enzyme; IDH, isocitrate dehydrogenase; PDH, pyruvate dehydrogenase; SDH, succinate dehydrogenase; FH, fumarate dehydratase; GLS, glutaminase; GDH, glutamate dehydrogenase; ACLY, ATP citrate lyase; ACC, acetyl-CoA carboxylase; FAS, fatty acid synthase; PPP, pentose phosphate pathway; TCA, tricarboxylic acid cycle; CI-V, mitochondrial respiratory complexes I, II, III, IV, V; OAA, oxaloacetate; αKG, α-ketoglutarate, ROS, reactive oxygen species.

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