Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Genetics & Development

Mitochondrial pyruvate carrier function and cancer metabolism

Adam J Rauckhorst and Eric B Taylor

Metabolic reprogramming in cancer supports the increased biosynthesis required for unchecked proliferation. Increased glucose utilization is a defining feature of many cancers that is accompanied by altered pyruvate partitioning and mitochondrial metabolism. Cancer cells also require mitochondrial tricarboxylic acid cycle activity and electron transport chain function for biosynthetic competency and proliferation. Recent evidence demonstrates that mitochondrial pyruvate carrier (MPC) function is abnormal in some cancers and that increasing MPC activity may decrease cancer proliferation. Here we examine recent findings on MPC function and cancer metabolism. Special emphasis is placed on the compartmentalization of pyruvate metabolism and the alternative routes of metabolism that maintain the cellular biosynthetic pools required for unrestrained proliferation in cancer.

Address
Department of Biochemistry, Fraternal Order of the Eagles Diabetes Research Center, Abboud Cardiovascular Research Center, Holden Comprehensive Cancer Center, and Pappajohn Biomedical Institute, University of Iowa Carver College of Medicine, Iowa City, IA 52242, USA

Corresponding author: Taylor, Eric B (eric-taylor@uiowa.edu)

Current Opinion in Genetics & Development 2016, **38**:102–109

This review comes from a themed issue on **Molecular and genetic bases of disease**

Edited by **Jason Bielas** and **Carolyn Suzuki**

http://dx.doi.org/10.1016/j.gde.2016.05.003

Introduction

Cancer is characterized by aberrant metabolism that decouples biosynthesis and proliferation from normal cell cycle control. As recognized by Otto Warburg decades ago, a common feature of adaptive metabolism in cancer is high utilization of glucose, which supports cancer bioenergetics and biosynthesis in both normoxic and hypoxic environments. Indeed, increased glucose uptake is used as a clinical diagnostic to identify cancer *in vivo* by ^{18}fluorodeoxyglucose positron emission tomography [1]. However, cancer cells also require intact electron transport chain function and mitochondrial metabolism-dependent biosynthetic pathways [2,3•]. High rates of oxidative or reductive glutaminolysis frequently accompany increased glycolysis in cancer as mechanisms for supporting tricarboxylic acid (TCA) cycle-dependent biosynthesis when glycolytic carbon is directed away from mitochondrial metabolism [4]. Numerous mechanisms have been explored and demonstrated to contribute to elevated glycolysis in cancer. The reader is directed to several excellent reviews providing broad coverage of these mechanisms [5–7]. The purpose of this mini review is to highlight emerging research on the recently identified Mitochondrial Pyruvate Carrier (MPC) and the relationship between the critical metabolic decision of mitochondrial pyruvate uptake and overarching adaptive mechanisms in cancer metabolism.

The Mitochondrial Pyruvate Carrier

The Mitochondrial Pyruvate Carrier (MPC) conducts pyruvate from the cytosol into the mitochondrial matrix. The import of pyruvate into mitochondria is a critical metabolic decision because it links glycolysis, which does not require oxygen, with mitochondrial oxidative phosphorylation. The MPC biochemical activity was first measured in 1971 [8]. In 1977, a report on MPC function in cancer found that isolated mitochondria from Ehrlich hyperdiploid ascites tumor cells displayed an MPC activity with a decreased V_{max} but unchanged K_m relative to rat liver mitochondria [9]. The decreased MPC V_{max} in tumor cells was accompanied by a 20-fold decreased rate of pyruvate oxidation. A subsequent study in 1983 observed similar results in Ehrlich ascites tumor cells and also found that MPC activity was decreased in Morris hepatoma tumors [10]. However, mechanistic studies to understand the specific biochemical basis for decreased MPC activity and the potential contribution to aerobic glycolysis were hindered by lack of a molecular identity.

The genes encoding the MPC protein complex were recently identified, which now enables targeted molecular-genetic studies on MPC function [11,12]. The *MPC1* and *MPC2* genes encode two obligate protein subunits of the MPC, MPC1 and MPC2 respectively. These proteins form a heteroligomeric complex of currently undetermined stoichiometry in mammalian systems [11,13,14]. Both proteins are required for activity because loss of one leads to destabilization and loss of the other and thus loss of the MPC complex [11,12,14].

An important event contributing to the molecular identification of the MPC was the observation of a patient with an in-born error in pyruvate metabolism not explained by

decreased pyruvate dehydrogenase or pyruvate carboxylase activity [15]. Fibroblasts from this patient displayed greatly decreased ability to oxidize pyruvate. This phenotype was reversed when the cells were disrupted but not when permeabilized, suggesting an error in mitochondrial pyruvate uptake [15]. The causative mutation was subsequently identified to be in the *MPC1* gene, which resulted in a change of a highly conserved arginine residue to tryptophan [11].

Recent molecularly targeted investigations of the MPC have identified important functional contributions to both gluconeogenesis in diabetes [16,17] and proliferation in cancer [18••,19••,20••], which share the common pathology of excessive biosynthesis. For broad coverage of pyruvate metabolism and historical overviews of scientific advances on understanding of MPC function beyond the intended scope of this work, the reader is referred to several review articles [21–26].

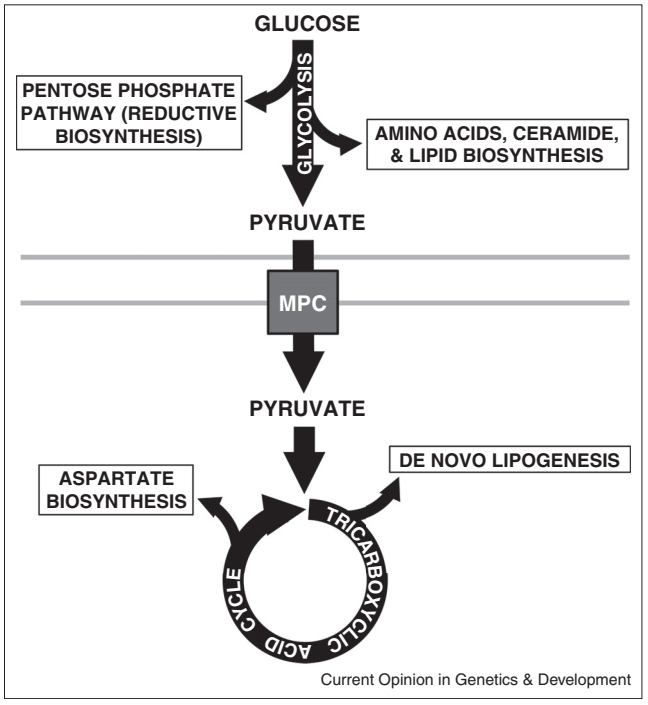
Mechanisms by which decreased MPC activity promotes cancer

Glycolytic support of biosynthesis

High rates of glycolysis enable cancer growth under both normoxic and hypoxic conditions. Glycolysis produces ATP, supports biosynthesis of triglycerides, ceramides, amino acids, and nucleotides for proliferation (Figure 1), and contributes to immune cell evasion and metastasis by acidifying the local tumor environment [6,27–29]. The first glycolytic intermediate, glucose 6-phosphate, may be either channeled for continued glycolytic oxidation or biosynthetic metabolism by the pentose phosphate pathway. Flux of glucose into the pentose phosphate pathway produces ribose for nucleotide synthesis and NADPH for reductive biosynthesis and maintenance of reduced glutathione and thioredoxin pools for defense against reactive oxygen species [30,31]. Further glycolytic breakdown of glucose 6-phosphate to fructose 1,6-bisphosphate followed by aldol cleavage produces dihydroxyacetone phosphate for phospholipid and triacylglycerol biosynthesis and 3-phosphoglycerate for the biosynthesis of amino acids and ceramide [6]. Reduction of dihydroxyacetone phosphate produces glycerol 3-phosphate that is acylated to generate phosphatidic acid upstream of the synthesis of di-acylglycerol and triacylglycerol, membrane lipids, and lipid signaling molecules [32]. Finally, a three-step process reduces, transaminates, and hydrolyzes 3-phosphoglycerate to serine, which supplies the polar head group and amide linkage for the *de novo* synthesis of ceramide and participates in protein synthesis [33].

The terminal step of glycolysis is catalyzed by pyruvate kinase, which converts phosphoenolpyruvate (PEP) to pyruvate. In some cancers the M2 isoform of pyruvate kinase (PKM2), typically a tetramer, is upregulated and adopts a dimeric form [34]. Dimeric PKM2 has decreased affinity for PEP such that at physiological concentrations of PEP the enzyme is essentially inactive (Figure 2a). Loss of PKM2 activity could lead to the accumulation of PEP, however this may be avoided by an alternative glycolytic pathway wherein PEP donates phosphate to the catalytic histidine of phosphoglycerate mutase generating pyruvate [35]. Yet even with this partial outlet for PEP removal, inactive PKM2 could promote the accumulation of other glycolytic intermediates. However, the high biosynthetic rate of rapidly proliferating cancer cells functions as a sink for these intermediates and prevents mass action-driven allosteric inhibition of glycolysis, thus preserving glycolytic flux [36].

Figure 1



Glycolysis and the TCA cycle are linked by a common molecule, pyruvate, and the activity of the MPC, which conducts pyruvate across the mitochondrial inner membrane. Glycolytic and TCA cycle intermediates support biosynthetic pathways: Glycolysis provides electrons in the form of glucose 6-phosphate to the pentose phosphate pathway for reductive biosynthesis. Dihydroxyacetone supports phospholipid and triacylglycerol biosynthesis. 3-Phosphoglycerate supports production of amino acids and ceramide. The TCA cycle generates citrate that supports cytoplasmic production of acetyl-CoA for *de novo* lipogenesis. Oxaloacetate may be transaminated to aspartate for amino acid biosyntheses.

Lactate production enables cancer bioenergetics and tumorigenesis

Complete breakdown of glucose to pyruvate may also promote cancer when coupled to its reduction to lactate. Lactate dehydrogenase A (LDHA) reduces pyruvate to lactate and simultaneously oxidizes NADH to NAD+,