PERSPECTIVE

During hypoxia, ageing HepG-2 cells complete the Krebs cycle by switching from the aminotransferase glutaminolytic pyruvate utilisation pathway

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ABSTRACT

A Hepatocellular carcinoma in humans HepG2 cells are forced to undergo Oxidative Phosphorylation (OXPHOS) when grown in aglycemic conditions with galactose and glutamine.These OXPHOS cells serve as a prototype for cancer cells' combined aerobic glycolysis and OXPHOS bioenergetics. It was our goal to identify the portions of the glutaminolytic pathway that involved the aminotransferase reaction that supplied 2-oxoglutarate (2OG) to the Krebs cycle active segment with Aconitase And Isocitrate Dehydrogenase-3 (ACO-IDH3), which is typically inactive in cancer cells because citrate is exported from the mitochondria. At normoxia, the aminotransferase inhibitor Aminooxyacetate (AOA) or AOA combined with the glutamate-dehydrogenase inhibitor Bithionol reduced OXPHOS cell respiration to 15% and 10%, respectively.When combined with AOA, the ratio of phosphorylating to non-phosphorylating respiration decreased from >6.5 to 1.9 and then to nil. Thus, glutaminolysis plays a major role in normoxic OXPHOS HepG2 cells. The immediate partial restoration of respiration upon addition of membrane-permeant dimethyl-2-oxoglutarate to inhibited cells demonstrated the absence of 2OG-dehydrogenase substrate post aminotransferase inhibition.Surprisingly, the AOA (bithionol) inhibition stopped after 72 hours of 5% O2 hypoxia, and respiration was fully recovered. As a result, the glycolysis pathway in diabetic HepG2 cells was accelerated by the Hypoxia-Induced Factor (HIF), which was preceded by galactolysis. Pyruvate was then redirected toward ACO-IDH3 via the still partially blocked pyruvate dehydrogenase. A greater activity of the Leloir pathway in OXPHOS cells was clearly matched by an increase in the glycolytic flux under hypoxia. NADPH oxidase activity was raised 2-fold in hypoxic OXPHOS cells but decreased in hypoxic glycolytic cells. At 5 mM glucose, OXPHOS cells and glycolytic cells experienced a reduction in; Contrary to aglycemic cells, glycolytic HepG2 cells showed the conventional HIF-mediated adaptation when exposed to hypoxia, i.e., even with unlimited respiratory substrate availability for 72 hours at 5% O2. Nevertheless, dm2OG significantly increased their ATP content compared to when it wasn't present during hypoxic adaptation. Thus, under conditions frequently established for solid tumours in vivo, such as aglycemia and hypoxia, the metabolic flexibility of cancer cells is demonstrated. Therefore, it is wrong to widely accept the exclusive and irreversible Warburg phenotype in cancer cells.

Key Words: *Aminotransferase; Dehydrogenase; Non-Phosphorylating; Isocitrate Dehydrogenase; Glutamine; Hepatocellular*

INTRODUCTION

Cells go through stages of gene expression reprogramming and mutagenesis during malignant transformation, which change their metabolic phenotypes. Dysregulated metabolism is thus one of the characteristics of cancer. It is common to establish a partly glycolytic "Warburg" phenotype (aerobic glycolysis). The ineffective conversion of pyruvate into lactate at the expense of pyruvate supply to the Krebs cycle during this partial glycolytic transition results in inadequate glucose oxidation, which causes Oxidative Phosphorylation (OXPHOS) to decline or go dormant. A developing tumour experiences hypoxia in some areas due to excessive proliferation and inadequate angiogenesis, which often results in the stabilisation of Hypoxia-Induced Factor-1 (HIF-1) and subsequent metabolic reprogramming by the HIF system, including encouragement of aerobic glycolysis.

By switching to the Pyruvate Kinase Muscle isoform (PKM) and inhibiting Mitochondrial Pyruvate Dehydrogenase (PDH) through PDH kinase-mediated PDH phosphorylation, HIF further enhances the glycolytic phenotype.

Numerous cancer cell types maintain OXPHOS to some extent despite this suppression of pyruvate entry into the Krebs cycle, most notably by glutaminolysis. As a result, glutaminase converts glutamine to glutamate. If Glutamate Dehydrogenase (GDH) is not severely inhibited as in typical glutaminolytic cancer cells, glutamate may be oxidised to 2-Oxoglutarate (2OG). Instead, 2OG is directly supplied

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by aminotransferase anaplerotic reactions to the Krebs cycle's 2OG-dehydrogenase during glutaminolysis.

Alanine aminotransferases (also known as glutamate pyruvate transaminases, GPT1 and GPT2) catalyse the reversible conversion of pyruvate plus L-glutamate to 2OG and L-alanine during glutaminolysis. These enzymes are found in the cytosol and mitochondria, respectively. Similar to this, oxaloacetate plus L-glutamate are transformed into 2OG and then L-aspartate by the aspartate aminotransferases AST1 and AST2 (also known as glutamate oxaloacetate transaminases, GOT1 and GOT2). Glutamate and a branched-chain 2-oxoacid are converted to a branched-chain amino acid and 2OG by the mitochondrial Branched-Chain Amino Acid Aminotransferase (BCAT), which is found in all tissues.

Both ALT1 and ALT2 use pyruvate, for which lactate dehydrogenase is their rival. If glutaminolysis didn't exist, acetyl-CoA would always be in limited supply during hypoxia, when the usual HIF transcriptome reprogramming also inhibits PDH. The Krebs cycle and oxidative phosphorylation would halt if this inhibition were fully effective. Glutaminolysis can inhibit the Krebs cycle at citrate synthase, resulting in unemployed forward Aconitase And Isocitrate Dehydrogenase-3 (ACO-IDH3) activity and ensuring citrate outflow to the cytosol. Because the cytosolic ATP-citrate lyase process converts citrate to oxaloacetate and Acetyl-CoA, and the resulting Acetyl-CoA serves as a precursor for lipid synthesis, cancer cells can maintain a high rate of cell proliferation. While mitochondrial transhydrogenase, malic enzyme, glutamate dehydrogenase, and IDH2 produce NADPH in the matrix, cytosolic isocitrate dehydrogenase IDH1, malic enzyme, and Glucose-6-Phosphate (G6P) dehydrogenase processes give NADPH within the cytosol. Under some circumstances, reductive carboxylation glutaminolysis, which consists of a reverse process inside the ACO-IDH3 segment and is supported by IDH2 and ACO, also contributes to the citrate efflux.