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Mitochondrial substrates in cancer: Drivers or passengers?

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ABSTRACT

The majority of cancers demonstrate various tumor-specific metabolic aberrations, such as increased glycolysis even under aerobic conditions (Warburg effect), whereas mitochondrial metabolic activity and their contribution to cellular energy production are restrained. One of the most important mechanisms for this metabolic switch is the alteration in the abundance, utilization, and localization of various mitochondrial substrates. Numerous lines of evidence connect disturbances in mitochondrial metabolic pathways with tumorigenesis and provide an intriguing rationale for utilizing mitochondria as targets for anti-cancer therapy.

1. Introduction

For decades, the role of mitochondria in cancer was vastly underestimated by the research community, which focused primarily on cancer genetics and ignored the seminal findings by the German biochemist and Nobel Laureate Otto Warburg, who hypothesized as early as 1927 the importance of these organelles for tumorigenesis (Warburg et al., 1927). Discoveries in recent decades have clearly confirmed his hypothesis, showing that disturbances of mitochondrial functions are not only key features of cancer, but also of other, mainly neurodegenerative, disorders, e.g., Parkinson's, Alzheimer's, and many other diseases. The importance of mitochondria under pathological conditions stems from their central role in many vital physiological processes in the cell, including ATP production, calcium homeostasis control, and reactive oxygen species (ROS) production, as well as in the execution and regulation of different cell death modalities. Not only have mitochondria come to the researcher's focus because of their role in various pathologies, but they are also regarded as promising targets for therapeutic interventions in these diseases.

Not only do mitochondria facilitate energy production in the form of ATP, but the majority of metabolic pathways are also directly or indirectly linked to these organelles. The driving force for most mitochondrial functions is the mitochondrial membrane potential, which is mandatory for ATP production, mitochondrial calcium accumulation, and other physiological pathways. The proton gradient is built up by proton pumps in the complexes of the electron transport chain and is fueled by electrons, which are provided by the reducing agents NADH and $FADH_2$. These reducing equivalents arise from the citric acid or tricarboxylic acid (TCA) cycle, which is the most important cellular metabolic network for oxidation of various energy sources, such as glucose, glutamine, and lipids. Many of the countless catabolic metabolic pathways merge at the level of the TCA cycle, fueling both energy production and anabolic processes by providing building blocks for the synthesis of amino acids and other important cellular components. The mitochondrial metabolic network comprises a large number of enzymes, as well as their specific substrates, which are located in the mitochondrial matrix, integrated into the inner- or outer mitochondrial membrane, intermembrane space or even in the cytosol, linked to the mitochondria via transporters and specific pumps (Fig. 1). This network is highly tunable and flexible, allowing the cell to adjust to different intra- and extracellular conditions, such as nutrient starvation, hypoxia, or other forms of cellular stress. One of the most important regulatory mechanisms for adjusting metabolic pathways is the modulation of the availability of mitochondrial substrates, which serves as a sensor for specific cellular conditions, and at the same time as a feedback loop for fine-tuning the enzymatic activities.

Metabolic dysregulation in cancer has long been regarded as a mere by-product of tumorigenesis to support tumor growth and survival. As mentioned above, originating from the findings of Otto Warburg, and after a rediscovery in recent years, it became more and more apparent that metabolic changes in cancer cells are not only a consequence of malignant transformation, but seem to be essential for this process and are regarded as a crucial hallmark of cancer (Hanahan and Weinberg, 2011).

Most cells utilize glucose as their main energy source, which is metabolized after its uptake in a set of glycolytic enzymatic reactions to form pyruvate. In normal cells, under normoxic conditions, most of the ATP is produced via oxidative phosphorylation (OXPHOS) in the mitochondria, whereas in cancer cells there is a shift towards glycolysis

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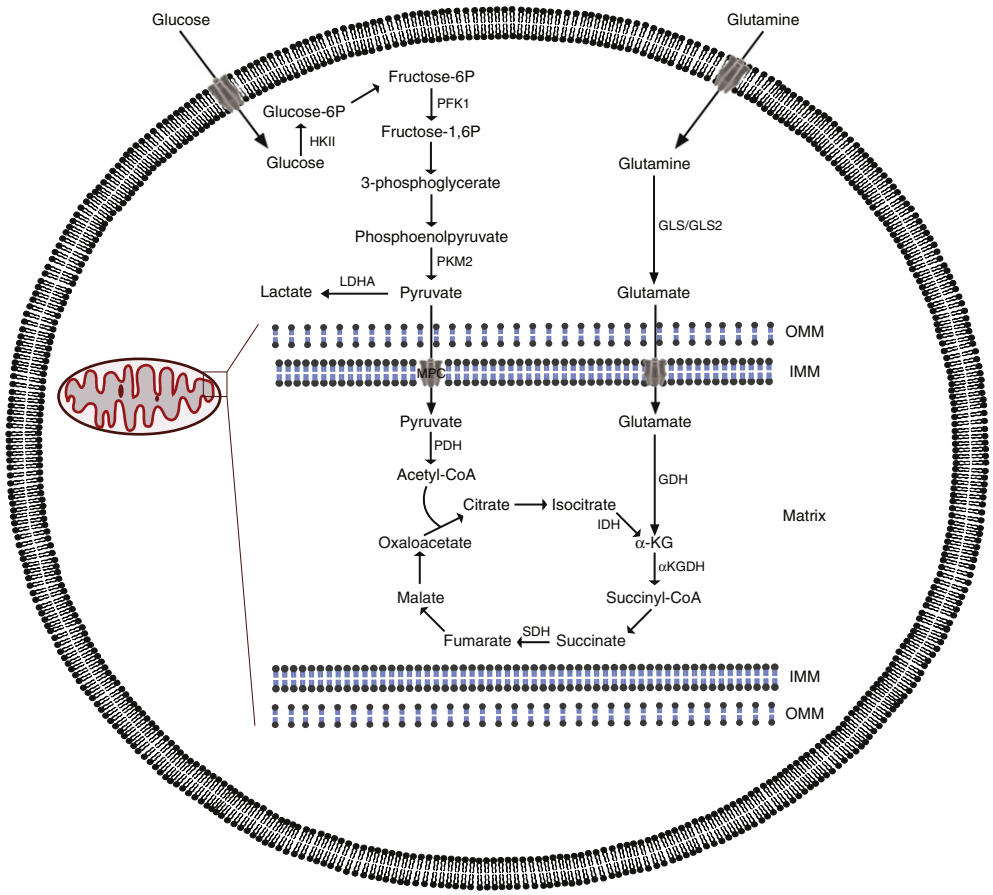

Fig. 1. Cellular glucose and glutamine metabolism. Overview of cellular glucose and glutamine metabolism, as well as the mitochondrial tricarboxylic acid cycle. Metabolic enzymes that are discussed within this review are indicated.
Figure adapted from BioCarta.

and suppression of mitochondrial function. This metabolic shift is mainly mediated by changes in the fate of pyruvate, the end-product of glycolysis. In normal cells, pyruvate is directed to the mitochondria where it is metabolized by pyruvate dehydrogenase (PDH) to enter the TCA cycle and fuel OXPHOS. In contrast, in most tumor cells, the activity of PDH is suppressed, causing a reduced flow of pyruvate to the mitochondria, and a decrease in OXPHOS. Under these conditions pyruvate is mainly converted to lactate by lactate dehydrogenase (LDH). Named after Otto Warburg, the "Warburg Effect" can be found in the majority of tumors. The reliance of tumor cells on glucose is even used for diagnostic purposes in fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) and therapeutically by utilizing the non-metabolizable glucose analog 2-deoxyglucose to block glycolysis and cancer growth. Glycolysis, despite being less efficient in terms of ATP yield per glucose molecule when compared to OXPHOS-driven energy production (2 vs. 36 molecules of ATP), renders tumor cells more resistant to oxygen-deprivation as a result of excessive growth or high metabolic activity and poor oxygen supply. It provides the cell with resources to sustain proliferation. For a long time, it was assumed that these metabolic changes are caused by defects in mitochondria but were, in fact, later found to be based on specific metabolic regulatory signaling. Thus, the phosphoinositide 3-kinase (PI3K) (Jiang et al., 2001) and mammalian target of rapamycin (mTOR) (Wouters and Koritzinsky, 2008) pathways were shown to induce a pseudo-hypoxic state independently of oxygen tension by stabilization of the hypoxia-inducible factor 1α (HIF1α), which causes a strong increase in glycolysis known as the Warburg phenotype.

Ultimately, different utilization, abundance, and localization of mitochondrial substrates might lead to tumor-specific adaptations of cellular metabolic pathways. The aim of this article is to give an overview of the current knowledge about the role of mitochondrial substrates in cancer development and their utilization as targets for potential therapeutic approaches.

2. Mitochondrial substrates in cancer

2.1. Pyruvate

The metabolic intermediate and glycolytic end-product pyruvate is a crucial switch between aerobic and anaerobic metabolism, and also serves as an important precursor for glucose, amino acid, and lipid synthesis. The fate of pyruvate is mainly determined by its subcellular localization. The main cytosolic catabolic reaction is mediated by LDH, reducing pyruvate to L-lactate, and at the same time producing one molecule of ATP and regenerating NAD^+, a critical cofactor for glycolysis function at the glyceraldehyde-3-phosphate dehydrogenase (GAPDH) level (Icard et al., 2012). In contrast, when metabolized in the mitochondrial matrix, pyruvate is oxidized to fuel the TCA cycle and OXPHOS. Under normoxic conditions, the majority of pyruvate is directed towards the mitochondria by an active transport through the inner mitochondrial membrane, mediated by the mitochondrial pyruvate carrier (MPC) (Halestrap, 1975), thereby linking the cytosolic glycolytic pathway with the mitochondrial TCA cycle. Within the mitochondrial matrix, PDH, a second key enzyme for this process, catalyzes the conversion to acetyl-CoA, NADH, and carbon dioxide. Acetyl-CoA thereafter enters the TCA cycle and ultimately fuels OXPHOS.

As mentioned earlier, a characteristic of a majority of cancers is the switch from oxidative, mitochondrial carbon metabolism to a reductive,