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Mini-review

The Warburg effect in tumor progression: Mitochondrial oxidative metabolism as an anti-metastasis mechanism

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ABSTRACT

Compared to normal cells, cancer cells strongly upregulate glucose uptake and glycolysis to give rise to increased yield of intermediate glycolytic metabolites and the end product pyruvate. Moreover, glycolysis is uncoupled from the mitochondrial tricarboxylic acid (TCA) cycle and oxidative phosphorylation (OXPHOS) in cancer cells. Consequently, the majority of glycolysis-derived pyruvate is diverted to lactate fermentation and kept away from mitochondrial oxidative metabolism. This metabolic phenotype is known as the Warburg effect. While it has become widely accepted that the glycolytic intermediates provide essential anabolic support for cell proliferation and tumor growth, it remains largely elusive whether and how the Warburg metabolic phenotype may play a role in tumor progression. We hereby review the cause and consequence of the restrained oxidative metabolism, in particular in the context of tumor metastasis. Cells change or lose their extracellular matrix during the metastatic process. Inadequate/inappropriate matrix attachment generates reactive oxygen species (ROS) and causes a specific type of cell death, termed anoikis, in normal cells. Although anoikis is a barrier to metastasis, cancer cells have often acquired elevated threshold for anoikis and hence heightened metastatic potential. As ROS are inherent byproducts of oxidative metabolism, forced stimulation of glucose oxidation in cancer cells raises oxidative stress and restores cells' sensitivity to anoikis. Therefore, by limiting the pyruvate flux into mitochondrial oxidative metabolism, the Warburg effect enables cancer cells to avoid excess ROS generation from mitochondrial respiration and thus gain increased anoikis resistance and survival advantage for metastasis. Consistent with this notion, pro-metastatic transcription factors HIF and Snail attenuate oxidative metabolism, whereas tumor suppressor p53 and metastasis suppressor KISS1 promote mitochondrial oxidation. Collectively, these findings reveal mitochondrial oxidative metabolism as a critical suppressor of metastasis and justify metabolic therapies for potential prevention/intervention of tumor metastasis.

Introduction: the Warburg effect in cancer

Altered metabolism is a universal property of most, if not all, cancer cells [1,2]. One of the first identified and most common biochemical characteristics of cancer cells is aberrant glucose metabolism. Glucose is a main source of energy and carbon for mammalian cells, providing not only energy (ATP) but also metabolites for various anabolic pathways [3]. Glucose is taken up into the cell by glucose transporters and metabolized to pyruvate in the cytosol through a multi-step process known as glycolysis, which also yields a small amount of ATP. In normal (quiescent) cells, the glycolysis-derived pyruvate is predominantly imported into the mitochondrial matrix where it is oxidized to acetyl coenzyme A (CoA) by the pyruvate dehydrogenase (PDH) complex. Acetyl CoA is then fed into the tricarboxylic acid (TCA) cycle,

Abbreviations: 2-DG, 2-deoxy-D-glucose; CoA, coenzyme A; COX, cytochrome c oxidase; DCA, Dichloroacetate; EMT, epithelial-to-mesenchymal transition; ERR, estrogen-related receptor; ETC, electron transport chain; F1, 6BP, fructose 1,6-bisphosphate; F2, 6BP, fructose-2,6-bisphosphate; F6P, fructose-6-phosphate; FAO, fatty acid oxidation; FBP1, fructose-1,6-biphosphatase 1; FDG, 18-fluorodeoxyglucose; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; GSH, reduced glutathione; HIF, hypoxia-inducible factor; IMS, mitochondrial intermembranous space; ISCU, iron-sulfur cluster assembly protein; LDH, lactate dehydrogenase; MnSOD, manganese superoxide dismutase; MOMP, mitochondrial outer membrane permeabilization; NAD+, nicotinamide adenine dinucleotide; NAMPT, nicotinamide phosphoribosyltransferase; OXPHOS, oxidative phosphorylation; PDH, pyruvate dehydrogenase; PDK, pyruvate dehydrogenase kinases; PDP, pyruvate dehydrogenase phosphatases; PET, positron emission tomography; PFK, phosphofructokinase; PKM, pyruvate kinase; PPP, pentose phosphate pathway; ROS, reactive oxygen species; TCA, tricarboxylic acid.

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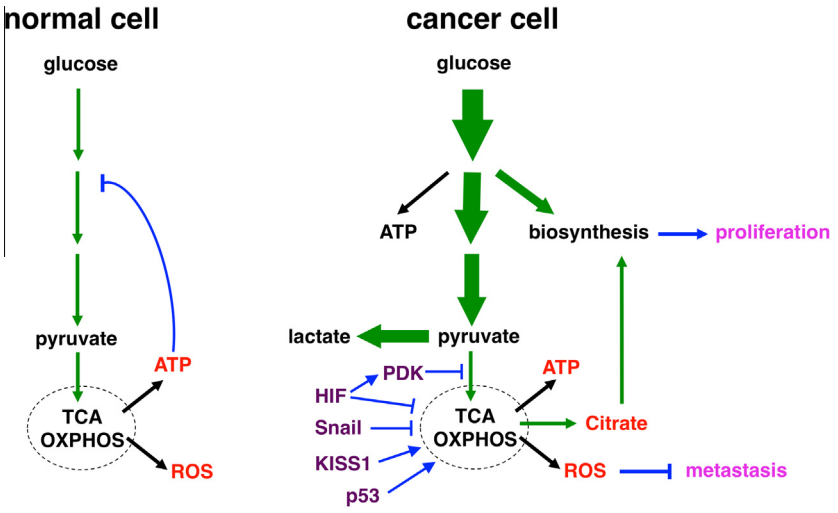

Fig. 1. Schematic illustration of glucose metabolism in normal and cancer cells under normoxia. (left) In normal (quiescent) cells, glucose is converted to pyruvate through glycolysis, and most pyruvate enters mitochondrial oxidative metabolism for efficient energy generation (in the form of ATP). Glucose is predominantly used for energy production. High levels of ATP attenuate glycolysis *via* feedback inhibition. (right) Cancer cells dramatically increase glucose uptake and glycolysis (indicated by bold arrows). A significant portion of glucose carbon is diverted to biosynthetic pathways to fuel cell proliferation. Pyruvate is preferentially shunted to lactate, resulting in increased lactate production. Oxidative metabolism persists, but is uncoupled from increased glycolysis. The respiration byproducts ROS exhibit anti-metastasis activity, which may explain why cancer cells keep glucose oxidation in check. The flux of glucose carbon is indicated by green arrows (The thickness of arrows reflects the relative amount of the flow). Major mitochondrial products are depicted in red; metastatic regulators are in purple; regulatory steps are in blue; and the metabolic effects on cancer are in pink. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

followed by oxidative phosphorylation (OXPHOS) for high-efficiency ATP generation. The full oxidation of one molecule of glucose produces up to 38 ATP molecules (including 2 ATP generated by glycolysis).

By contrast, most cancer cells show conspicuous alterations in glucose metabolism (Fig. 1): (i) Compared to normal cells, cancer cells typically exhibit drastically increased glucose uptake and glycolytic rates. Increased glucose consumption generates more intermediate glycolytic metabolites and a significant amount of ATP from glycolysis. (ii) Moreover, a substantial fraction of glucose carbon, in the form of assorted glycolytic intermediates, is shunted into multiple biosynthetic pathways instead of giving rise to pyruvate. (iii) Finally, following glycolysis, most pyruvate is converted to lactate in the cytoplasm by the action of lactate dehydrogenase (LDH) and secreted, rather than being oxidized through mitochondrial metabolism. This occurs even in the presence of sufficient oxygen to support mitochondrial respiration. The metabolic phenomenon was first described by Otto Warburg and is referred to as aerobic glycolysis or the "Warburg effect" [4]. Although human cancers display a diverse range of metabolic profiles [5], the Warburg metabolic phenotype is a widespread cancer-associated trait. Indeed, enhanced glucose uptake by cancer cells has become the basis for positron emission tomography (PET) with 18-fluorodeoxyglucose (FDG), which preferentially accumulates in tumor cells as a result of their rapid uptake of glucose. Because of the prevalence of this phenotype, PET is an effective clinical imaging technique to detect most cancers and monitor therapeutic responses.

It is noteworthy that mitochondrial function in most cancer cells is intact. Warburg observed that the absolute rate of mitochondrial respiration in cancer cells remains comparable to that of normal cells [4]. Oxidative metabolism indeed persists in the vast majority of tumors and remains a major source for ATP generation [6,7]. Nevertheless, while there is a profoundly elevated flux of glucose in cancer cells, it is predominantly directed to lactate fermentation, and the flow to oxidative metabolism does not increase proportionally. Simply put, increased glucose consumption in cancer cells is devoted to lactate conversion and biosynthesis, and is uncoupled from oxidative metabolism. In fact, there exist regulatory mechanisms downregulating oxidative metabolism of glucose in cancer cells (see below). Since a considerable portion of observed oxygen consumption in cancer cells may be attributed to oxidation of alternate fuels such as glutamine [8,9], the actual glucose oxidation in cancer cells is probably even lower.

The cause and consequence of the Warburg effect have been at the center of cancer metabolism study. Cancer is a disease arising from genetic and epigenetic alterations in oncogenes and tumor suppressors, many of which are also able to reprogram metabolism. The metabolic changes occurring in cancer were thus considered a secondary effect to the transformation process. However, as rapid cell proliferation requires accelerated production of the basic cellular building blocks for assembling new cells, it has now become well recognized that alterations in cellular metabolism in turn fuel tumor growth by maximally producing substrates for biosynthesis [3]. Glycolytic breakdown of glucose produces various intermediate metabolites, which as precursors can be diverted into anabolic pathways including the pentose phosphate pathway (PPP), serine and triacylglycerol synthesis pathways for the *de novo* synthesis of nucleotides, amino acids, and lipids [10]. While normal cells metabolize glucose almost exclusively for maximal energy production (though full energy extraction deprives cells from biosynthesis of building blocks), cancer cells boost glucose consumption primarily to provide a constant supply of glycolytic intermediates to satisfy the anabolic need of dividing cells. In this regard, glycolytic intermediates seem to be more important than the final product pyruvate. Cancer cells indeed use a variety of strategies to slow down the last step of glycolysis that is catalyzed by pyruvate kinase (PKM) [11], allowing buildup of glycolytic intermediates for biosynthesis. The altered glucose metabolism thus favors the conversion of glucose into biomass and sustains the highly proliferative nature of cancer [3]. Taken together, while alterations in oncogenes and tumor suppressors drive inappropriate cell proliferation, they also concomitantly rewire and coordinate cellular metabolism to meet the biosynthetic demands of continuous cell division.

Although the proliferative advantage offered by the Warburg metabolic phenotype is well established, its significance in metastatic progression has been much less clear. Moreover, if the

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