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Review Article

Lipid metabolism and cancer progression: The missing target in metastatic cancer treatment

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ABSTRACT

There is a renewed interest in metabolism alterations and its impact on cancer development and progression. The metabolism of cancer cells is reprogrammed in order to support their rapid proliferation. Elevated fatty acid synthesis is one of the most important aberrations in cancer cell metabolism, and is required both for carcinogenesis and cancer cell survival. We have previously shown that cancer cells explore metabolic pathways especially autophagy and particularly enhanced glycolysis and suppressed oxidative phosphorylation to promote treatment resistance. To support cell proliferation in cancer, lipid metabolism and biosynthetic activities is required and often up-regulated. Here we bring lipid metabolic pathways into focus and summarized details that suggest a new perspective for improving chemotherapeutic responses in cancer treatment, and indicate the need to design more inclusive molecular targeting for a better treatment response.

Introduction

The earliest report of Otto Warburg about 100 years ago that cancer cells exhibited dysregulated metabolism compared with normal cells, lead to a hypothesis that molecular oxygen defects in cells results in a slow adaptation to enhanced aerobic glycolysis and may constitute a metabolic switch that caused cancer (Warburg, 1956). The enhanced aerobic glycolysis exhibited by some cancer cells provides them with a characteristic signature and results in increased dependence on glucose (Omabe et al., 2013). Thus, Warburg effect is a distinctive feature of many human and animal tumors (Omabe et al., 2013). In majority of cancers, glucose is converted mostly to lactate (Fig. 1), and, therefore, only 2 moles of ATP per 1 mole of glucose are synthesized, which is therefore insufficient for

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cancer cells to cope with its energy requirements. However, in most non-cancer cells, the mitochondria produce CO_2 and H_2O from glucose, and 38 moles of ATP are synthesized per 1 mole of glucose from the oxidative metabolism under aerobic conditions (Omabe et al., 2013).

From glucose metabolism to fatty acid biosynthesis

Full detail of glucose metabolism can be found in appropriate textbook of Biochemistry. The understanding of metabolism forms a unique component of practice for Chemical Pathologist. In brief, following cellular uptake by glucose transporters, glucose is phosphorylated by hexokinases to glucose-6-phosphate (Figs. 1 and 2). Most of glucose-6-phosphate enters the glycolytic pathway to generate pyruvate and ATP. Pyruvate is converted to acetyl coenzyme A (CoA), and enters the citric acid cycle in the mitochondria (Omabe et al., 2013). Depending on the oxygen availability citrate can be fully oxidized to generate ATP by oxidative phosphorylation, or it can be transported to the cytoplasm where it is converted back to acetyl-CoA (the requisite building block for fatty acid (FA) synthesis) by ATP citrate lyase (ACLY). Under anaerobic conditions pyruvate can also be used as an electron acceptor, resulting in the lactate dehydrogenase (LDH)-catalyzed production of lactate, which is secreted from the cell. A portion of the acetyl-CoA is carboxylated to malonyl-CoA by acetyl-CoA carboxylase (ACACA), the primary rate-limiting enzyme and site of pathway regulation. Fatty acid synthase (FASN), the main biosynthetic enzyme, performs the condensation of acetyl-CoA and malonyl-CoA to produce the 16-carbon saturated FA palmitate and other saturated long-chain FAs, which is dependent on NADPH as a reducing equivalent. NADPH (which is essential for FA synthesis) is provided in a reaction catalyzed by malic enzyme, or can be acquired through the pentose phosphate pathway. Saturated long-chain FAs can be further modified by elongases or desaturases to form more complex FAs, which are used for the synthesis of various cellular lipids such as phospholipids, triglycerides and cholesterol esters, or for the acylation of proteins. Elevated activities of citrate synthase (CS) and ACLY are observed in some malignancies, hence, inhibition of ACLY is known to lead to cessation of tumor growth (Schlichtholz et al., 2005; Vazquez-Martin et al., 2009). This is because cell proliferation requires a constant supply of lipids and lipid precursors to fuel membrane biogenesis and protein modification. In this review, we searched a number of available literatures through Medline, pub med, Google scholar and EMBO search engine using key words like cancer metabolism, fatty acid, cytokines and metastasis. This work therefore highlights a synthesis, and focused on the role of adipocytes derived molecules and lipid metabolism in cancer progression, and underscored current understanding toward exploring this physiologic phenomena

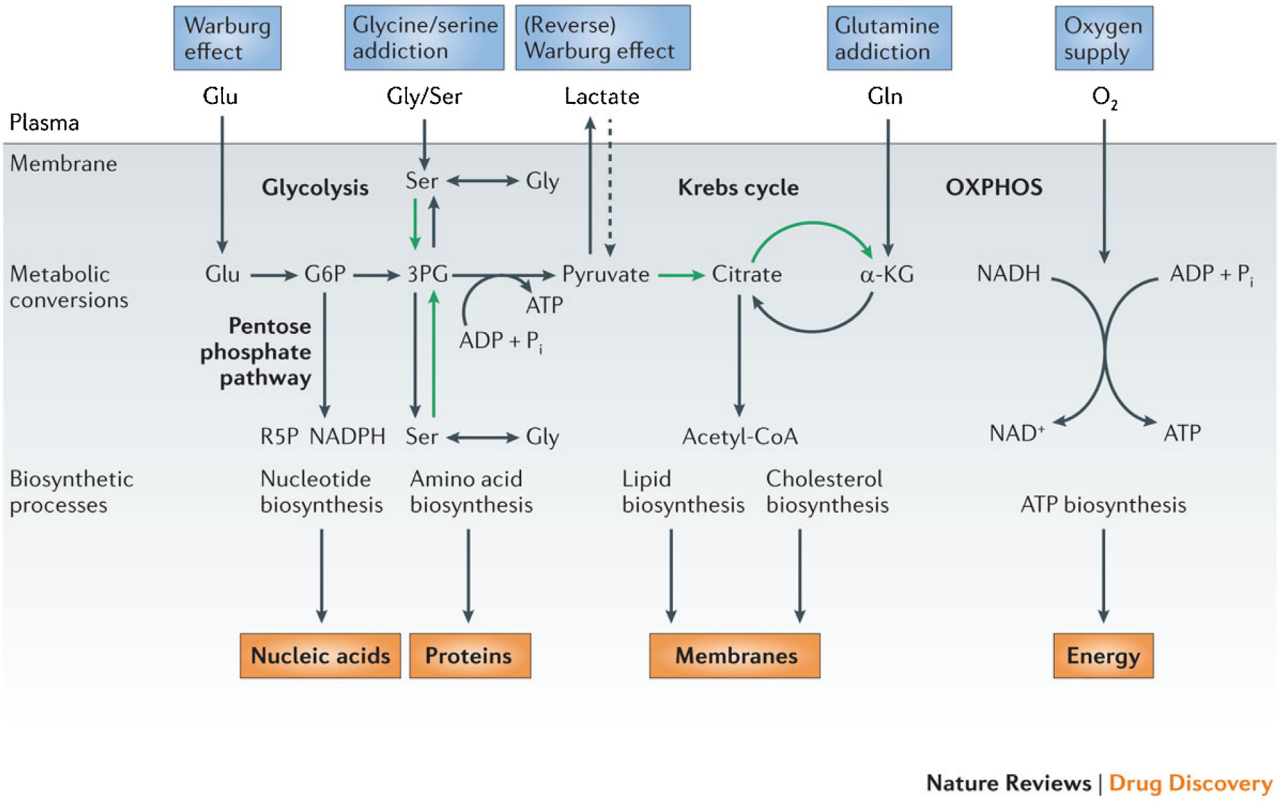

Fig. 1 – Malignant cells exhibit a profound imbalance toward anabolic metabolism. Cancer cells take up high amounts of glucose (Glu; underpinning the Warburg effect) and glutamine (Gln) and divert them to the phosphate pentose pathway and lipid biosynthesis, respectively. Coupled to an increased uptake of glycine (Gly) and serine (Ser), which are required for protein synthesis and sustain anaplerotic reactions that replenish Krebs cycle intermediates, this generates sufficient building blocks (that is, nucleic acids, proteins and membranes) for proliferation.
Source: **Adapted from Galluzzi et al. (2013).**