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Review

Yeast and cancer cells – common principles in lipid metabolism

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ABSTRACT

One of the paradigms in cancer pathogenesis is the requirement of a cell to undergo transformation from respiration to aerobic glycolysis – the Warburg effect – to become malignant. The demands of a rapidly proliferating cell for carbon metabolites for the synthesis of biomass, energy and redox equivalents, are fundamentally different from the requirements of a differentiated, quiescent cell, but it remains open whether this metabolic switch is a cause or a consequence of malignant transformation. One of the major requirements is the synthesis of lipids for membrane formation to allow for cell proliferation, cell cycle progression and cytokinesis. Enzymes involved in lipid metabolism were indeed found to play a major role in cancer cell proliferation, and most of these enzymes are conserved in the yeast, *Saccharomyces cerevisiae*. Most notably, cancer cell physiology and metabolic fluxes are very similar to those in the fermenting and rapidly proliferating yeast. Both types of cells display highly active pathways for the synthesis of fatty acids and their incorporation into complex lipids, and imbalances in synthesis or turnover of lipids affect growth and viability of both yeast and cancer cells. Thus, understanding lipid metabolism in *S. cerevisiae* during cell cycle progression and cell proliferation may complement recent efforts to understand the importance and fundamental regulatory mechanisms of these pathways in cancer.

Contents

1. Introduction

In their review "The Hallmarks of Cancer", Hanahan and Weinberg [1] defined six alterations in cellular processes that are required to turn a normal cell into a cancer cell: response to growth and antigrowth signals, prevention of apoptosis and senescence, induction of angiogenesis, and the ability to colonize other body parts. These milestones in cancer development, however, are exclusively addressing regulatory and signaling processes. In a recent update of their work, the authors expanded their list of required modifications for cancer development by two novel – emerging – hallmarks, namely defense against immune destruction and modifications in energy metabolism [2]. The latter – energy metabolism – is in fact a trait, which has been described in some detail already in the twenties of the last century. Otto Warburg published his observations that the metabolism of cancer cells is shifted from the oxidation of glucose to carbon dioxide and respiration-driven ATP production to fermentative reduction of pyruvate to lactate. Under these conditions,

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ATP is mainly derived from cytosolic glycolysis, which, however, is a much less efficient pathway to generate energy compared to mitochondrial respiration [3]. Only a few years later, Herbert G. Crabtree showed that mitochondrial respiration in neoplastic tissue is repressed at physiological glucose concentrations [4]. Warburg concluded from his seminal work that cancer cells develop due to defective mitochondrial respiration, forcing the cell to shift to aerobic fermentation, even if oxygen supply is not limiting [5]. Although it has been shown meanwhile that cancer cells are not necessarily compromised in respiratory activity, the switch to high glucose uptake rates and fermentative metabolism is still considered a property of almost all types of tumors [6,7]. The reasons for this physiological switch remain a matter of debate. Reduction of the metabolic flux from pyruvate to lactate results in sensitivity of cancer cells to hypoxic conditions and impaired growth [8]. However, it is unclear whether aerobic glycolysis is a prerequisite for a cell to become neoplastic or if this dramatic switch in metabolism occurs concomitantly to, or after malignant transformation. It has also been suggested that aerobic glycolysis that is accompanied by high glucose uptake rates and acidification of the extracellular environment, is a response to hypoxic conditions and may provide a growth advantage. Similarly, aerobically fermenting yeasts, which convert glucose to ethanol and acetic acid at high rates, prevent competing microorganisms from growth, while being tolerant to high ethanol concentrations and low pH themselves [9]. In addition, reduced mitochondrial activity might contribute to the ability of cancer cells to evade apoptosis. Although aerobic glycolysis generates only 2 mol of ATP per mol of glucose, the overall rate of ATP production might indeed be higher in aerobic glycolysis than in mitochondrial respiration, due to lower costs for enzyme production or higher activities of the fermenting enzymes, compared to tricarboxylic acid (TCA) cycle and respiratory chain enzymes and cofactors [10,11].

2. Cell proliferation: Energy requirements and biomass production

By considering metabolic fluxes it becomes obvious that a rapidly proliferating cell not only relies on sufficient supply of energy in the form of nucleoside triphosphates, but also on a sufficient flux of glucose- or amino acid-derived metabolites into biosynthetic pathways to fuel the duplication of biomass during every cell cycle (Fig. 1). In addition to the consumption of energy and carbon precursors, these biosynthetic activities require numerous anaplerotic reactions, especially in the TCA cycle, and the maintenance of a redox balance for the major redox cofactors, NAD^+/NADH and $NADP^+$/NADPH. Since the production of biomass from glucose-derived metabolites is mainly a reductive process that requires NADPH for the synthesis of amino acids and lipids, pathways for reduction of $NADP^+$ have to be activated and the cytosolic NADH has to be rapidly re-oxidized to maintain high glycolytic rates. In contrast, a differentiated non-proliferating cell has no or only minor activity of anaplerotic biosynthetic pathways and can fully oxidize glucose to obtain the maximum possible ATP yield. This demand for a balanced supply of energy, redox equivalents and biomass precursors at high rates may provide an explanation for the switch of cancer cells to aerobic glycolysis, accompanied by high rates of glucose uptake and catabolism.

In an attempt to simulate the growth behavior and physiology of a cancer cell with constraint based flux balance analysis (FBA), Shlomi et al. showed that their metabolic model switched from respiration to aerobic glycolysis at high specific growth rates when a constraint for the enzyme solvent capacity of the cellular milieu was introduced [12]. In this simulation, kinetic constants of metabolic enzymes were introduced to allow for the computation of required enzyme concentrations at a given specific growth rate. A shift from respiration with high ATP yield to low yield overflow metabolism occurs when the enzyme concentrations and their respective turnover numbers are in favor of glycolysis, even if this results in a loss of carbon conversion efficiency [12]. Similar results are obtained by FBA with metabolic models of *Saccharomyces cerevisiae*, although in most of these simulations uptake of oxygen is used as a constraint to shift cells from respiration to fermentation [13], a behavior that is known as the Crabtree effect in yeast.

S. cerevisiae is often considered an organism that is almost entirely committed to fermentative metabolism. Thus, the physiology of a yeast cell and a proliferating cancer cell is very similar with comparable metabolic fluxes in these two cell systems [14]. It has to be noted, however, that the degree to which cancer cells are commited to aerobic glycolysis can vary in a broad range, but not to the same extent as in yeast, where respiratory activity is rather low in the presence of glucose. Aerobic glycolysis in yeast relies on high glucose concentrations: when yeast is cultivated in continuous culture under steady state conditions (chemostat) with glucose as the limiting nutrient, cells gradually switch to respiration when the dilution rate (i.e. the rate of nutrient supply) is reduced: at dilution rates of 0.1 h^{-1}, i.e. at a specific growth rate $\mu = 0.1\ h^{-1}$, metabolism of yeast is fully respiratory. Indeed, aerobic glycolysis is absent in yeast cultures at glucose concentrations in the range of physiological serum glucose levels in humans (~1 g L^{-1}), but is gradually induced when the glucose concentration is increased above this value. Due to this behavior yeast is a good model to study changes on transcriptional or posttranslational levels or in metabolic fluxes that are associated with the transition from respiration to fermentation [15–17]. The Crabtree effect is genetically determined and reversible in yeast, whereas the Warburg effect in cancer cells seems to be a consequence of spontaneous mutations; it is noteworthy, however, that development of cancer and mortality correlate with blood glucose levels in many cases [18–22]. Hence, increased glucose levels seem to be associated with the switch of neoplastic cells from respiration to aerobic glycolysis, as is also the case in yeast.

Irrespective of the as yet unknown molecular mechanisms that lead to the reprogramming of central carbon metabolism, this transformation apparently provides cancer cells with growth and/or survival advantages that are necessary for their rapid proliferation and invasiveness. Since this metabolic switch has been recognized as an indispensable feature of neoplastic tissue, genes involved in metabolism have become promising targets for cancer therapy; accordingly, the involvement of cellular metabolism in the development and progression of cancer has gained increased attention in recent years. Although mammalian cells are able to take up all major biomass constituents – glucose, amino acids, fatty acids, cholesterol – from the bloodstream, proliferation of cancer cells seems – at least in part – to rely on the endogenous synthesis of these components, as indicated by the metabolic switch to fermentation.

The major metabolic fluxes in a proliferating cell are dedicated to the synthesis of proteins and lipids, whereas only minor fluxes contribute to the synthesis of other components of biomass, such as nucleic acids. Hence, lipid metabolism has an essential function in biomass generation, and is also a major determinant of the cellular redox status. Furthermore, several steps in lipid synthesis have been recognized as being crucial for rapidly growing cancer and also for yeast cells, emphasizing again the metabolic similarities between both types of cells. In the following, we will review in greater detail glycerolipid synthesis and its interconnection with glycolytic fluxes and cellular redox balance, in both yeast and cancer cells.

3. Lipids in yeast and mammals: Functional conservation and structural differences

The basic pathways for the synthesis of membrane glycerolipids are identical in yeast and mammalian cells (Fig. 2), resulting in the same classes of phospholipids (PL), namely phosphatidic acid, phosphatidylinositol, phosphatidylserine, phosphatidylethanolamine, phosphatidylcholine, phosphatidylglycerol, and cardiolipin. Excess fatty acids (FA) that are derived from endogenous *de novo* synthesis, lipid turnover or nutritional supply are stored as triacylglycerol (TAG) in cytosolic lipid droplets, keeping the total amount of cellular phospholipids within a narrow