Biomedicine & Pharmacotherapy 89 (2017) 288–296

Available online at
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Review

Interplay between cancer cell cycle and metabolism: Challenges, targets and therapeutic opportunities

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ARTICLE INFO

Article history:
Received 28 October 2016
Received in revised form 2 January 2017
Accepted 2 January 2017

Keywords:
Cell cycle
Metabolism
Glycolysis
Pyruvate
PFKFB3
ErbB2

ABSTRACT

A growing interest has emerged in the field of studying the cross-talk between cancer cell cycle and metabolism. In this review, we aimed to present how metabolism and cell cycle are correlated and how cancer cells get energy to drive cell cycle. Cell proliferation and cell death largely depend on the metabolic activity of the cell. Cell cycle proteins, e.g. cyclin D, cyclin dependent kinase (CDK), some pro-apoptotic and anti-apoptotic proteins, and P53 have been shown to be regulated by metabolic crosstalk. Dysregulation of this cross-talk between metabolism and cell cycle leads to degenerative disorder(s) and cancer. It is not fully understood the actual reason of aberration between metabolism and cell cycle, but it is a hallmark of cancer research. Herein, we discussed the role of some regulatory molecules relative of cell cycle and metabolism and highlight how they control the function of each other. We also pointed out, current therapeutic opportunities and some additional crucial therapeutic targets on these fields that could be a breakthrough in cancer research.

Contents

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http://dx.doi.org/10.1016/j.biopha.2017.01.019
0753-3322/

1. Introduction

1.1. Importance of cross talk between cell cycle and metabolism in cancer research

Cancer is uncontrolled cellular growth and proliferation. In order to maintain high growth rate, cancer cells utilize additional nutrients, which is provided by sufficient generation of ATP. All cancer cells depend on this altered metabolism [1], and this aberrant metabolism produces huge amounts of energy which drives cell cycle unendingly. Progression of cell cycle in order to altered metabolism is a crucial therapeutic target [2,3]. It has been studied widely that some biological molecules and enzymes play major role in progression of metabolic process to generate huge ATP that act as a source of energy of cell cycle progression [2,3]. Our aim is, to normalize the metabolic process and slow down the magnitude of metabolic rate in cancer cells by mediating key molecules, which is greatly impact on regulation of cell cycle. It is an attractive therapeutic target in cancer research.

1.2. ATP as a source of energy

Cell cycle progression depends on the availability of energy that is directly proportional to cell growth and proliferation. Similarly deprivation of energy is inversely proportional to cell growth. Required energy for driving cell cycle is provided through glycolysis. In cancer cells, increase in rate of glycolysis is mediated by several biological molecules and the rate of ATP generation is enhanced that is linked to cell cycle progression and cell proliferation. Extracellular glucose is internalized into cells by glucose transporters (GLUTs) and then intracellular glucose is phosphorylated to glucose-6-phosphate (G6P) which is further converted to pyruvate and two molecules of ATP are generated via the action of several enzymes. On the other hand, Acetyl CoA enters to the citric acid cycle and produces 36 molecules of ATP in the presence of oxygen [4]. ATP is crucial for many biological processes such as synthesis, transportation, degradation of biological molecules and drives cell cycle and cell growth [5,6]. Its also has an important role in regulating the metabolic pathways. In most eukaryotic cells, whereas glycolysis produces two molecules of ATP [7]. In most eukaryotic cells, 36 molecules of ATP are generated by aerobic respiration from 1 glucose molecule. 2 molecules of ATP from glycolysis, 2 molecules from citric acid cycle substrate level phosphorylation and 32 molecules from electron transport by oxidative phosphorylation [8]. ATP generated from glycolysis is the main source of energy for initiation of cell cycle.

Final summary of aerobic respiration:

$$C_6H_{12}O_6 + 6O_2 + 36\ ADP + 36\ Pi \rightarrow 6\ CO_2 + 6\ H_2O + 36\ ATP$$

1.3. Cancer cells prefer glycolysis over the citric acid cycle for energy generation

Citric acid cycle is aerobic metabolism that occurs in the mitochondria and generates most of the ATP molecules from the glucose [7]. Normally cancer cells avoid citric acid cycle because it occurs in the mitochondria; and mitochondrial process is associated with apoptosis through cytochrome c and caspase-dependent pathways, but cancer cells need uncontrolled growth to proliferate rapidly [9]. Cancer cells produce pyruvic acid more

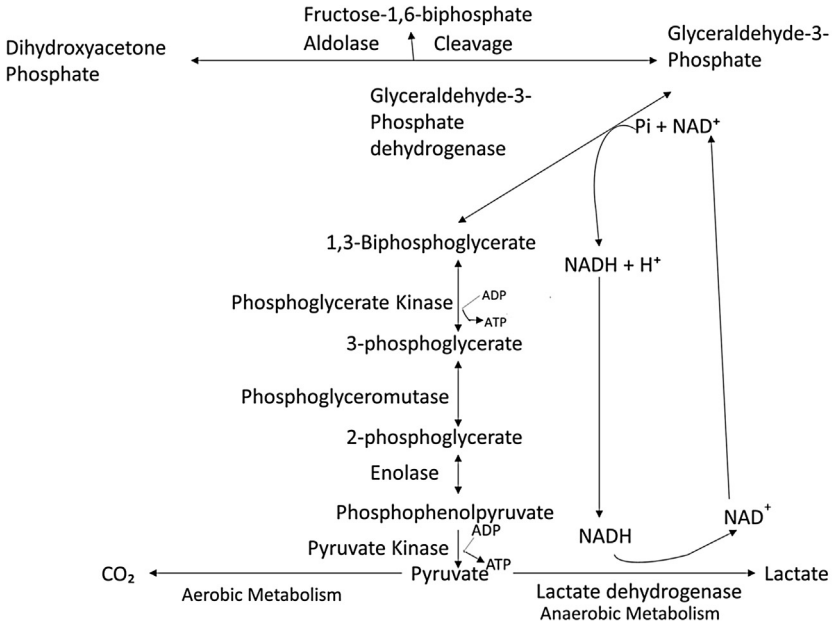

Fig 1. In aerobic metabolism, by the action of lactate dehydrogenase-A (LDH-A), pyruvate is converted to lactate and generated NAD^+ which is recycled and utilized for the conversion of glyceraldehyde-3-Phosphate to 1,3-biphosphoglycerate. By this way NAD^+ maintains unending glycolysis process in cancer cell.