Journal of Oncological Sciences 3 (2017) 45–51

Contents lists available at ScienceDirect

Journal of Oncological Sciences

journal homepage: https://www.elsevier.com/locate/jons

Biology of glucose metabolization in cancer cells

Adewale Fadaka*, Basiru Ajiboye, Oluwafemi Ojo, Olusola Adewale, Israel Olayide, Rosemary Emuowhochere

Department of Biochemistry, College of Science, Afe Babalola University, Ado-Ekiti, Ekiti State, Nigeria

ARTICLE INFO

Article history:
Received 12 April 2017
Received in revised form
3 June 2017
Accepted 14 June 2017
Available online 19 July 2017

Keywords:
Cancer
Glucose
Glycolysis
Hypoxia
Warburg

ABSTRACT

Cancer is a disease at the cellular level involving heritable disorders in cellular control mechanism. Cancer cells also need to adapt their metabolism to survive and multiply under the metabolically compromised conditions provided by the tumor microenvironment. Tumor cells alter their metabolism to maintain unregulated cellular proliferation and survival, but this transformation leaves them reliant on constant supply of nutrients and energy. They alter their metabolism to support their rapid proliferation and expansion across the body. After the discovery of based on the altered cancer cell metabolism in 1930, loads of studies have shed light on several aspects of cancer metabolism with a common goal to find new ways for effectively eliminating tumor cells by targeting their energy metabolism. Research has directed most of its resources to elucidate the causes, prevention and possible cure for cancer, yet the process has been elusive claiming human lives more than ever. This disease is a manifestation of etiological and pathological disturbances of mechanisms that control cell division, differentiation and metabolism. 50% of all human tumors carry genetic alterations that lead to the inactivation of some tumor suppressor proteins. Cancer cells are shown to experience characteristic changes in their metabolic programs, including increased uptake of glucose, enhanced rates of glutaminolysis and fatty acids synthesis, suggesting that metabolic shifts supports tumor cells growth and survival. In this review, we summarized the major concepts of glucose metabolization and explore the molecular basis of aerobic glycolysis of cancer cells.

1. Introduction

There has been an enigmatic search of information on the mechanism of cancer related metabolic adaptations, and this has resulted in accumulated evidences suggesting considerable association between several pathways in human metabolism and malignant transformation.[1–3] Carcinogenesis is a complex, multistep process requiring the elimination of several cell-imposed barriers such as anti-proliferative responses, programmed cell death-inducing mechanisms, and senescence. This occurs mostly through genetic alterations in oncogenes and tumor suppressor genes.[4] In other for the body to prevent the growth of tumor, there is chronic activation of the immune system. These two processes (tumor growth and immune system activation) are responsible for an increased energy usage and thus for continuous consumption of energetic substrates, such as carbohydrate.[5] In fact, the oxidation of glucose into CO_2 and H_2O through the citric acid cycle is a well-known major source of energy and plays a key role in the biosynthesis of ATP, constituent of DNA, RNA and phospholipids. Glucose is also necessary for the pentose phosphate pathway and the synthesis of reducing compounds such as NADPH. Energy metabolism in advanced tumor cells is severely compromised by the occurrence during the disease progression of symptoms such as nausea anorexia, and vomiting, which does not allow normal nutrition and therefore, a regular supply of carbohydrates, proteins, amino acids and vitamins. Reduced oral intake resulting from anorexia or obstruction of the gastrointestinal tract plays a crucial role in the development of the cancer cachexia syndrome. In addition to the reduced food intake, important changes of energy metabolism and biochemical/metabolic abnormalities in carbohydrate, protein and lipid biochemistry and metabolism have been observed, which may account for cancer-related anorexia/cachexia syndrome.[6] Altered energy metabolism consisting of increased resting energy expenditure associated with increased metabolism of sugar, lipid and

* Corresponding author.
E-mail addresses: fadakaao@abuad.edu.ng, silvernonferous@gmail.com (A. Fadaka).

Peer review under responsibility of Turkish Society of Medical Oncology.

http://dx.doi.org/10.1016/j.jons.2017.06.002

protein metabolism are typical of cancer cells. These changes are a consequence of alterations in intermediary metabolism (carbohydrate, protein, and lipids) associated with cancer. Also, activation of oncogenes and deactivation of tumor suppressor genes, have been associated to cancer-associated metabolic remodeling of epigenetic marks.[7]

2. Overview of carbohydrate metabolism in normal cell

Carbohydrates constitute a major part of our diet and our food is the ultimate source of all the sugars that enter our metabolic pathways. About two-thirds of dietary carbohydrate is the plant polysaccharide. Disaccharides such as lactose and sucrose and some other polysaccharides like cellulose are also a part of our food, but our intake of free monosaccharide like glucose, fructose and galactose is relatively reduced.[8]

Carbohydrate metabolism starts with digestion in the small intestine when monosaccharides are absorbed into the blood stream. Blood sugar concentrations are controlled by three hormones: insulin, glucagon, and epinephrine. If the concentration of glucose in the blood is increased insulin is released from the pancreas. Insulin stimulates the transfer of glucose into the cells in the liver and muscles, in the liver and muscles most of the glucose is converted to glycogen, a process known as glycogenesis. Glycogen is stored in the liver and muscle. The breakdown of glycogen to glucose is called glycogenolysis. The metabolites from glycolysis form links with protein, lipid and nucleic acid. Glucose is the central molecule in carbohydrate breakdown and synthesis. All major pathways of carbohydrate metabolism are connected to conversions of glucose, since glucose is the main sugar in the blood and the main energy fuel in the body. The metabolic pathways are glycolysis, Oxidation of Pyruvate, Citric Acid Cycle, Pentose Phosphate Pathway, Glycogen metabolism (glycogenolysis, glycogenesis) and Gluconeogenesis.

2.1. Glycolysis (Embden-Meyerhoff pathway) in normal cells

Glycolysis is a universal pathway for catabolism of glucose in animals and plants. It occurs in all cells of our body. The process (glycolysis) convert one molecule of glucose to two molecules of pyruvic acid, and the energy released is conserved in the form of ATP and reducing equivalent NADH. The main function or aim of glycolysis is to provide energy and intermediates for other metabolic pathways. The major sources of glucose for glycolysis are dietary carbohydrates and cellular glycogen. Glucose undergoes glycolysis by a sequence of 10 cytosolic reactions, seven of which are reversible while three are irreversible. The first five reactions constitute the “investment” phase since they use ATP, while the last five reactions constitute the “pay-off” phase and yield ATP. In glycolysis (normal cells), which happens in the cytoplasm, one glucose molecule yields 2 ATPs and 2 NADH molecules (NADH is another energy-carrying molecule), and two pyruvates. If oxygen is present, the two pyruvates, with help from the pyruvate dehydrogenase enzyme complex, is converted to two Acetyl-CoA molecules. The acetyl-CoAs enter the mitochondrion where it fuels the citric acid cycle. Each acetyl-CoA molecule goes through the citric acid cycle. Therefore, from one glucose, the yield is 6 NADH molecules, two $FADH_2$ molecules, and two ATP molecules. The 6 NADH +2 FADH, plus the NADH produced in glycolysis and at the PDH complex, now enter the “electron transport system” (ETS). This is where the efficient production of ATP occurs: The ETS is a multistage process, called oxidative phosphorylation or cellular respiration, which, with the help of ATP synthase has the following yield: This summary gives a theoretical yield of 40 ATP per glucose. 32–38 ATPs are generated depending on the enzymes an individual's DNA codes for. Cancer cells typically “switch” from “cellular respiration” to the very inefficient glycolysis for their ATP needs, a phenomenon described by Otto Warburg in 1924. The amazing thing is that tumors, which are highly energy demanding tissues, switch to a very inefficient energy producing pathway. They make up for this energy demand by going through glycolysis faster than necessary in normal cells.

2.2. Metabolizing pathways in cancer

Cancer is a disease condition arising from uncontrolled division of cells in the body to form lumps of tissues called tumors. There are many different types of cell in the body, and many different types of cancer which arise from different types of cell. Some are more easily treated than others, particularly if diagnosed at an early stage, some have a better outlook (prognosis) than others.[9] These cells may invade or spread to other parts of the body where they can go on proliferating and causing unhealthy condition to the system. Those cells with minimum uncontrolled growth and do not invade other cells are said to be benign while cells that grow and divide rapidly and as well invade other tissues are said to be malignant.

Normally, cells are expected to grow, divide and then die. In a situation where the deoxyribonucleic acid (DNA) of a cell is damaged by some factors, known as risk factors, and the cell cannot repair the damaged DNA, then it may not be able to control the normal programmed cell growth. This results to development of cancer. In each case, it is important to know exactly what type of cancer has developed, how large it has become, whether it has spread, and how well it usually responds to treatment. Cancer results from the development of abnormal properties in normal cells that enable them to grow excessively and spread to other locations. This abnormal development can be caused by mutations that occur from factors such as paints, chemicals, radiation, ultraviolet light and chromosome replication errors.[10] These mutagens alter DNA by changing nucleotide bases and can even change the shape of DNA. The altered DNA produces errors in DNA replication, as well as errors in protein synthesis. These changes influence cell growth, cell division, and aging. Viruses such as Human papilloma virus can cause cancer by altering cell genes though a class of cancer. Cancer viruses change cells by integrating their genetic material with the host cell's DNA.

2.2.1. The Crabtree effect

Crabtree made an observation on the utility of carbohydrates by cancer cells.[11] It was observed that, for normal cells, the presence of glucose slightly increased respiration or had no effect on oxygen consumption. On the contrary, glucose decreased oxygen uptake by cancer cells. This respiratory inhibition is known the Crabtree effect. It is now known that this metabolic transformation of cancer cells is not a specific feature of carcinogenesis, but appears to be a requirement of rapidly dividing cells such as proliferating hematopoietic progenitor cells, spermatozoa, intestinal mucosal cells, renal cells, and embryonic stem (ES) cells.[12] This phenomenon is also reported in bacteria and yeast. Apart from rapid proliferation, an important characteristic shared by all these cells, as will be expected from respiratory impairment, is increased glycolysis. Another observation of the Crabtree effect is the initial increase in respiration following the provision of glucose. Indeed, it appears that other hexoses can induce this effect in cancer cells as well. Several explanations have been provided based of the Crabtree effect, although the molecular mechanism is not fully understood. The mechanisms are as follows: (1) Competition for available ADP + Pi between oxidative phosphorylation and glycolysis can cause respiratory abnormalities by increased glucose availability.[13]