Clinics in Oncology

Review Article
Published: 06 Dec, 2017

Lactate: Metabolic Hallmark of Cancer in 21st Century

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Abstract

Current understandings of lactate and tumor metabolism indicate that lactate acts as both a potent fuel (oxidative) and signaling molecule (angiogenesis and immune-suppression) in the body. Tumors that exhibit a "Warburg Effect," are fueled by lactate through lactate shuttle. Reports suggest that the expression of LDH and the production of acidosis due to lactic acid from tumor cells facilitate the escape of cancer from immune surveillance. Cancer/germline (CG) antigens are promising targets for widely applicable mono and multi-antigen cancer vaccines for different cancers. While elevation of somatic LDH (LDH-A) is a well-studied marker in both solid and hematologic neoplasms, studies on cytogenetic changes of lung adenocarcinoma and their correlation with the role of LDH-C deserve future investigations. Sperm specific LDH-C, a cancer/testis antigen, and being highly immunogenicallo-antigen offers potential application in immunotherapy of cancers.

Introduction

From early work we developed the concept that the lactate is deemed waste product of glycolysis that must be cleared from the muscles and blood, preferably by being converted to glucose in the liver via Cori cycle. However, during last 50 years, it has been suggested that lactate is both a potent fuel and signaling molecule, which is being produced and circulated throughout the body, often when there is adequate O_2supply [1,2]. Despite several reports demonstrating that lactate has diverse metabolic effects, lactic acid is still considered as a waste metabolite of anaerobic glycolysis and being erroneously taught in medical books even this day.

Aerobic versus Anaerobic Glycolysis

Although unlike lactate metabolism, the study of tumors dates back to 1600 BC, the present era of tumor metabolism began with experiments conducted by Cori's and Otto Warburg in 1920s. Warburg showed that the vein always had more lactate and less glucose than the artery feeding the tumor, suggesting a net lactate output in presumably normoxic tumor beds. Otto Warburg clearly recognized the "Warburg Effect," an unusual behavior whereby tumors produce lactate in a normoxic environment [3].

Under aerobic conditions, normal cells metabolize glucose (the primary source of energy)to pyruvate via glycolysis in the cell cytosol, and subsequently convert pyruvate to carbon dioxide in the mitochondria for oxidative phosphorylation. Des-regulated proliferation of cancer cells is generally associated with altered energy metabolism. Under anaerobic conditions, conversion of pyruvate to lactic acid is favoured with relatively low amounts of pyruvate being diverted to the mitochondria. In contrast, cancer cells primarily derive energy from glucose via glycolysis to lactic acid, even under highly aerobic conditions, a process first observed by Otto Warburg. This 'aerobic glycolysis', also known as 'Warburg effect', is very less energy-efficient than the oxidative phosphorylation pathway [3].

In addition, cancer cells derive energy from up-regulated non-glucose-dependent pathways, such as increased glutaminolysis under aerobic conditions. Aerobic glycolysis and increased glutaminolysis are now accepted as key metabolic hallmarks of cancer. Both pathways lead to the production and secretion of lactic acid, markedly contributing to metabolic acidosis commonly found in solid cancers. There are plenty of reports showing the link between pH and cancer. Cancer thrives in an acidic environment, and doesn't survive in normal or alkaline conditions. Cancer cells make body even more acidic as they produce lactic acid. Extracellular pH values in tumors can be as low as pH 6.0-6.5, in contrast to pH 7.4 present in normal cell environments. Taking action to make your body more alkaline is vital in the battle against cancer. Actually, too much acidity is an underlying factor in many degenerative diseases, such as diabetes, renal failure, arthritis, fibromyalgia and others.

OPEN ACCESS

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Received Date: *02 Oct 2017*
Accepted Date: *25 Nov 2017*
Published Date: *06 Dec 2017*

Citation:
Gupta GS. Lactate: Metabolic Hallmark of Cancer in 21st Century. Clin Oncol. 2017; 2: 1375.

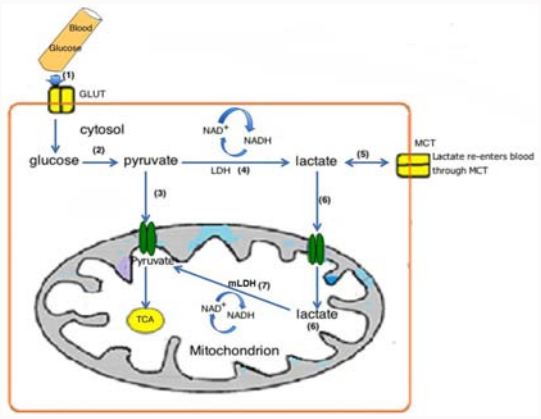

Figure 1: This suggests that targeting this metabolic pathway in tumors is a promising strategy to enhance tumor immunogenicity.

Lactate: A Signaling Metabolitein Cancer

All cancer patients have lactic acid in their bodies. When the patient starts to lose weight and starts to lose their appetite, due to their cancer, the cachexia is very serious. The body is full of lactic acid. The lactic acid cycle, commonly called "cachexia," occurs for following reasons:1) Cancer cells routinely create lactic acid.2) This lactic acid released by the cancer cells travels to the liver via the bloodstream.3)The liver converts the lactic acid into glucose.,4) The liver releases the glucose and cancer cells are likely to pick up this glucose because cancer cells consume about 15 times more glucose than normal cells [2].

A possible correlation between serum lactate levels and tumor burden in patients suffering from different tumor types has been found associated to suppressed proliferation of cytokine production, human **cytotoxic** T cell (also known as **cytotoxic** T lymphocyte, **CTL**s) generation and a decrease in cytotoxic activity. Blockade of mono-carboxylate transporter (MCT)-1resulted in impaired CTL function [1]. This suggests that targeting this metabolic pathway in tumors is a promising strategy to enhance tumor immunogenicity (Figure. 1).

Oxygen tension plays an important role in tumor progression. The hypoxia in the tumor environment up-regulates genes encoding glucose transporters and glycolytic enzymes such as LDH. Accordingly, tumor cells produce and secrete lactic acid, which in turn lowers the pH in the tumor environment. Most likely hypoxia-inducible factors (HIF-1α, HIF-2α), transcription factors that are induced either under hypoxic conditions or by cell pyruvate and lactate, which are produced in the process. HIF-1α and HIF-2α are expressed in the majority of human tumors. Gatenby and Gillies proposed that this "glycolytic phenotype" of tumor cells confers a growth advantage and is necessary for the evolution of invasive human cancers.

Low-oxygen, or hypoxic, cells cause resistance to radiation therapy. Hypoxic cells are also more difficult to treat with chemotherapy. Many tumors have cells that burn fuel for activities in different ways. Tumor cells near blood vessels have adequate oxygen sources and can either burn glucose like normal cells, or lactic acid (lactate). Tumor cells farther from vessels are hypoxic. In turn, they produce lactate as a waste product. It has been demonstrated that tumor cells with good oxygen supply actually prefer to burn lactate, which frees up glucose to be used by the less-oxygenated cells. But when we cut off the cells' ability to use lactate, the hypoxic cells didn't get as much glucose. While this may seem like a harmless cycle, about half of all cancer patients die due to high lactic acid for two reasons: i) the conversion of glucose to lactic acid by the cancer cells and the conversion of lactic acid to glucose in the liver both consume massive amounts of energy and II) the lactic acid itself, while it is in the bloodstream, can block key nutrients from reaching healthy cells (i.e. non-cancerous cells). Most often death is on account of damage to the non-cancerous cells.

The pyruvate to lactate reaction is catalyzed by lactate dehydrogenase (LDH), a rapid, near-equilibrium reaction that lies heavily in the direction of lactate. Lactate equilibrates mainly by transporting across membranes via monocarboxylate transporters into circulation, where both local and distant tissues can take it up and use it as a fuel. The observation that lactate is constantly being produced and consumed, George Brooks in 1984 put a hypothesis of 'lactate shuttle' which suggested that lactate is the key intermediate metabolite which is used as fuel in almost all body cells having mitochondria, including muscle, heart, liver and as well as in brain.

In addition to work as a fuel, recent reports have shown that lactate is also a potent signaling molecule, which triggers the stabilization of hypoxia inducible factor-1α (HIF-1α), and subsequently increasing expression of vascular endothelial growth factor (VEGF), resulting in angiogenesis. This new concept is now being explored in tumor models [1]. Angiogenic endothelial cells, like tumor cells, are largely dependent on aerobic glycolysis and increased glutaminolysis for energy. Moreover, lactic acid generated by the pathways has been found to markedly promote angiogenesis by increasing the production of interleukin-8/CXCL8, driving the autocrine stimulation of endothelial cell proliferation and maturation of new blood vessels. Lactate also has a role as a potent signaling molecule particularly in tumor metabolism, as high-lactate levels are often associated with a worse prognosis. Any change in lactate immediately equilibrates with pyruvate through LDH and vice versa. When lactate (pyruvate) levels increase, HIF-1α drives angiogenesis via VEGF expression [1]. It should be emphasized that HIF-1α stabilization can be driven by lactate or hypoxia independently. The lactate-to-VEGF pathway appears to be an appealing target for potential anti-tumor therapies. An *in vivo* study in mice, after lactate administration showed enhanced Xenografted tumor growth, metastasis, and vascularity [4-6]. In an effort to understand the role of lactate in the tumor microenvironment, it is found that tumors formed only within the cranial vault in mice, which is the area of highest lactate concentration in the mouse.

Current reports indicate that altered metabolism of lactate can also enhance the growth of cancer by promoting immune evasion on account of lowering of pH. The anti-cancer immune response, as it is mediated by effector T-cells, has long been known to depend on components of the micro-environment such as helper cells and cytokines. However, it is influenced by the environmental pH due to lactic acid; an acidic pH can markedly impede the function of normal immune cells. A lower environmental pH to 6.0-6.5 in tumor environment has been reported to lead to the loss of T-cell function of tumor-infiltrating lymphocytes; the T-cell function could be completely restored by buffering the pH to physiological value. The primary cause responsible for the acidic pH and pH-dependent T-cell function-suppressive effect in a tumor micro-environment is the presence of lactic acid. It has also been demonstrated that cancer-

generated lactic acid and the resultant acidification of the micro-environment increase the expression of ARG1 in tumor-associated macrophages, characteristic of the M2 helper phenotype. The locally suppressed immunity then serves as a basis for the establishment of the malignancy and its subsequent malignant progression.

Lactate Dehydrogenases: The Targets of Cancer Therapy

TetramericLDH-A and -Ccatalyse conversion of pyruvate and NADH to lactate and NAD^+ and play key roles in regulating glycolysis. Cancer cells commonly have up-regulated LDH-A and -C, which promote a metabolic switch to aerobic glycolysis and generate lactate as a product of glycolysis. While LDH-A is dominantly present in somatic tissues and cancer cells, LDH-C is dominantly expressed in testis in addition to cancer. The synthesis of LDH-C4 in the testis takes place during sexual maturation, and it is the predominant fraction in mature spermatozoa[4]. Though, originally considered to be testis specific, LDH-C or Ldh3 in mice was later detected in the murine oocyte and early embryo The sperm specific Ldh-c gene has been shown to express in a broad spectrum of humantumors, with high frequency in lung cancer [47%], melanoma [44%], and breast cancer [35%]; the protein resulting in significant expression in virtually all tumor types tested98 whereas LDH-A is considered to have a highest efficiency among all other isoenzymes to catalyse pyruvate transformation to lactate and is significantly overexpressed in several different tumor entities such as oral squamous cell carcinoma (OSCC). Both LDH-A and LDH-C have overlapping sequential specificities. Provided evidence that LDH-C enzyme acts as a cancer testis antigen (CTA) in breast carcinoma and exerts an essential role in tumor invasion and migration [1,5]. In a loss-of-function experiment LDH-C blocked with its specific inhibitor N-propyl oxamate, reduced the invasion and migration of MDA-MB-231 cells.

Several studies suggest that targeted down-regulation of LDH induce reactive oxygen species (ROS) and can inhibit tumor progression Tumor metastasis, a multi-step process, is tightly regulated by lactate and continues to cause more than 90% of human cancer deaths. Among glycolytic enzymes LDH-A is a potential enzyme which helps in promoting the metastasis [6]. By targeting LDH-A sensitizes cancer cells to anoikis induction and reduces the metastatic potential. Among glycolytic enzymes tyrosine phosphorylated LDH-A offers metabolic advantage to tumor growth [6]. The tyrosine phosphorylation of LDH-A at tyrosine 10 is commonly up-regulated in metastatic tumors compared to primary tumors [1,6].

Elevated LDH isa negative prognostic biomarker that allows neoplastic cells to suppress and evade the immune system by altering the tumor microenvironment. LDH-A alters the tumor microenvironment via increased production of lactate [1]. This leads to enhancement of immune-suppressive cells, such as myeloid-derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs), and dendritic cells (DCs); and inhibition of cytolytic cells, such as natural killer (NK) cells and cytotoxic T-lymphocytes (CTLs). By promoting immune-suppression [1] in the tumor microenvironment, LDH-A can promote resistance to chemo/radio/targeted therapy [1]. Elevation of LDH A is harbinger of negative outcome in both solid and hematologic neoplasms [1].

Targeting LDH-A and LDH-C [5] attenuates tumor growth and tumor metastasis [6]. LDH inhibitors including gossypol and its derivative FX-11, galloflavin and N-hydroxyindole-based compounds are being tested for their anticancer activity. One of the key substances that block the lactic acid from being created inside the cancer cells is cesium chloride. Cesium chloride literally accumulates inside the cancer cells. Hydrazine sulphate is another known substance which blocks the lactic acid cycle in the liver, where it blocks the creation of glucose from lactic acid. However, hydrazine sulfate has many safety rules to follow, especially the warnings to stay away from tranquilizers and certain amino acids. *Ldhc* gene located within 11p15 from tumors of smokers or male show significantly higher transcripts of *Ldhc* than non-smokers or female, respectively. The results indicated that different cytogenetic changes of malignant pleural effusions from lung adenocarcinoma are correlated with genders and smoking habits. The role of *Ldhc* in the carcinogenesis deserves further investigations. LDH-C, being an iso-, allo- and heterologous CT-antigen, is a promising antigen for immunotherapy of cancers [5].

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