

Review Article

Role of Lactic Acid in Cancer Metabolism Under the Influences on Tumor Expansion and Metamorphosis: A Review

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Abstract: Anaerobic glycolysis advertise the production of energy under hypoxic condition (absence of oxygen), while in aerobic glycolysis, the Warburg effect gives a momentous benefit through remodeling carbohydrates seeds from production of energy to biochemical pathways. On the other side, high degree of lactate have been cooperated with feeble outcome in human tumors as well as glycolytic switch is correlated with high rate of glucose uptake and lactate production. Although lactic acid was primarily remind as indicator of the glycolytic process in which many mechanisms initiates from the study of normal tissue physiology and transported to the tumor indicating lactic acid in essence lactate anion and protons, straightly contributes to tumor growth and development. MCT1 & MCT4 monocarboxylate transporters have been justified as well-known facilitators of lactate exchanges between various cancer cells with many metabolic behaviors. In this review, we summarize the current knowledge on the role of lactic acidosis and metastasis, lactate shuttles and lactate signaling molecules.

Keywords: Lactic Acid, Tumor Intrusion, Shuttles, Signaling Molecules

1. Introduction

All phenotypic lineaments like cellular structures, expressions of gene, growth, proliferation as well as metastatic efficacy shows cancers considerable heterogeneity. And this type of heterogeneity primarily associated to heritable changes in cancer-causing genes (oncogenes) and tumor suppressor genes. Normally, glucose molecules enter into the cells through some particular glucose transporters mainly GLUT1 & GLUT4. In glycolysis, pyruvate generate after phosphorylation by hexokinases and under aerobic case, with the help of pyruvate dehydrogenase reaction, acetyl-CoA migrate into the TCA cycle to be metabolized to CO₂. A momentous dimension of pyruvate is reduced into lactate in the presence of lactate dehydrogenase-5, and NADH is oxidizing into NAD in action of anaerobic glycolysis to correct the Glyceraldehyde-3-phosphate dehydrogenase

reaction by the heightened of pyruvate dehydrogenase kinase 1 enterprise that inhibit the pyruvate dehydrogenase activity [1, 2] through the conversion of malate into pyruvate by the presence of malic enzyme [3].

Lactate acts as a polar ion for the transfer of protons through lactate-proton symporter mono carboxylate transporter 4 (MCT4) [4]. Therefore, under hypoxia condition or anaerobic glycolysis gives the chances of high glucose consumption & enormous lactic acid release. The lactate elevation in cancer and tumor can definitely reach up to 40mM with an moderate elevation of 10 mM [5].

According to Warburg effect, tumor cells mainly in advanced cancers cells might represent aerobic glycolysis [6]. Under normoxic conditions, instead of getting cleaved the carbohydrates molecules, thus promoting the tumor cell growth and development. DNA synthesis and NADPH production, alanine synthesis from pyruvate indulge the pentose phosphate biochemical pathway as well as amino

acids synthesis and transportation.

Elated efficiency of FDG ([¹⁸F]-fluorodeoxyglucose) uptake shown high negative outcome in cancers causing patients [7, 8]. As a result, we address the modulation and conveyance of MCTs, highlighting MCT1 as a indigenous

tumor specific target and inhibition allows to disturb biochemical cooperatively and tumor angiogenesis with the same target and allow to create a natural or harmless anticancer therapies.

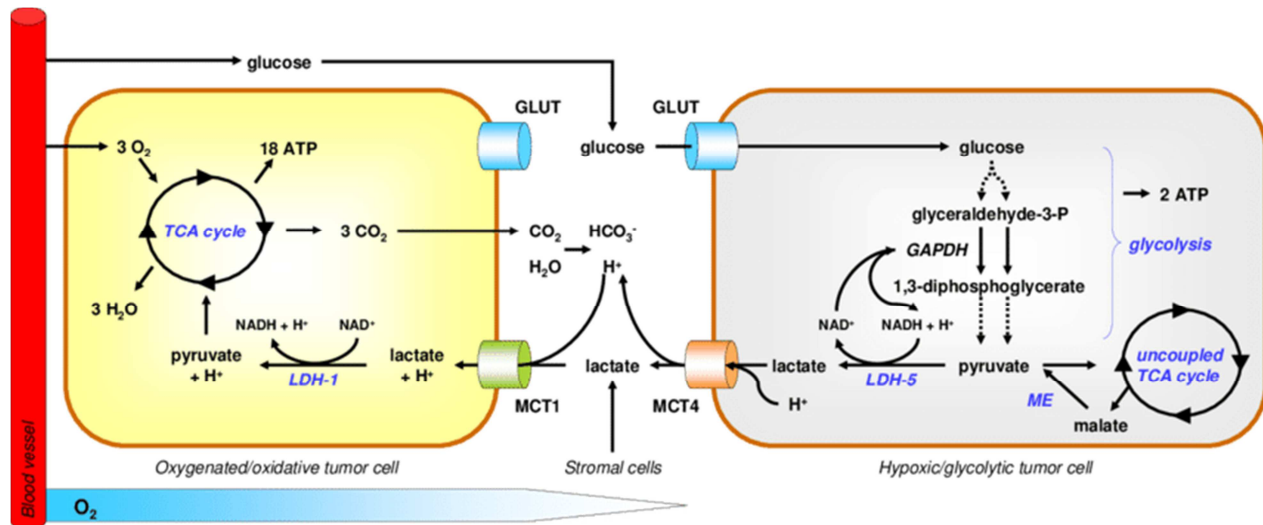


Figure 1. Mechanism of lactate shuttles in tumors.

1.1. Lactic Acid as a Tumor Surge Agent

Mostly lactate anions and protons are monomers of lactic acid in all biological fluids [9]. After completion of glycolysis cycle, lactic acid was end product which is responsible for muscle fatigue and shrinkage and it is also a major cause in acidosis-lured tissue catabolism. Gluconeogenesis is also known as Cori cycle explained the liver adopts lactate from the blood cells to undergo in Cori cycle [10]. The lactate activities in common tissues have only been observed in tumor perspective and also some evidence proves that lactate in tumor acts as a fuel for the electron transport chain of oxygenated tumor cells [11-16], and a signaling agent in tumor and endothelial cells [17-19].

1.2. Conveyor and Modulator of Lactate in Cancer

The conveyance of lactate is essential for tumors with inflated glycolysis which is also important for inhibit the cellular acidification by smuggle lactic acid. MCT1 plays a prominent role which mainly focuses on expressed in human glioblastoma & glioma derived cell lines and MCT2 also plays same role in tumor cells. And MCT4 modulates the growth and trafficking of CD147 to the cell membrane [20] whereas in Caco-2 cells & knockout of MCT1 leads to prior of the immature and core glycosylated form of CD147 [21]. And MCT 3D structure also called chaperons might exist and CD44 was certainly exposed to immunoprecipitate to modulate the intracellular trafficking of MCT1 and MCT4 in cancer cells of breast [22].

Lactate is present in the form of anion and needs conveyors to penetrate cell membrane and transportation function is predominantly exerted by the MCT family. Normally, MCTs are proton coupled proteins with both carbon and nitrogen

terminal tails existed in the cytosolic domain. CD147 also expressed endometrial carcinomas & esophageal squamous cell carcinomas in cancer cells which normal tissue don't express [23-25]. Metalloproteinase's 1, 2, 3, 9, 11 elevated CD147 in tumor causing cells leading to a rebound of the ECM cooperate tumor cells growth and cell mobility [26-28].

SLC5A transport family substrates also familiar to SLC16A MCT family couples that belongings to sodium coupled MCTs in which SMCT1 has strong affinity towards lactate and modulates the uptake of brief chain fatty acids in the colon [29] and the tubular resorption of lactate and glycolysis outcome (pyruvate) in the kidney [30]. Primarily, two molecules of pro-apoptotic (pyruvate & butyrate) serving as potent inhibitors of histones [31]. Like this SMTC1 don't expressed in many types of tumors, including thyroid, colon, brain, breast, and kidney cancers [32].

1.3. Metabolic Growth & Lactate Shuttles in Cancer

ATP is an energy source and muscle cells use fatty acids and glucose to generate high amount of ATP. Lactate uptake is also dependent on MCT process in which all the MCT types indulged and takes place the mechanism [33]. Normally, MCT1 and MCT4 are exposed by muscles in the presence of isoform-specific alignment & tissues such as heart and red muscles gives more expression of MCT1 whereas in glycolytic white muscles; MCT4 phenomenon was observed in large amount [34].

Between the glycolytic muscle fibers and oxidative muscle fibers where oxidation of pyruvate takes place through LDH-1, & MCT1 expression and the threshold access are mainly focusing point in which blood starts accumulate the lactate [35]. And mutual lactate shuttle is exposed between neurons in the brain. Recently studies exposed that lactate accumulate in

the blood is fervent consumer of brain tissue & lactate is referred metabolic substrate for neurons also in the presence of glucose [36, 37].

MCT1 & MCT4 both are exposed by astrocytes and perform aerobic glycolysis pathway and transport the substantial amount of lactate into the ECM. After that, lactate is consumed by surrounding neurons or brain cells by the high affinity of lactate modulator MCT2 exposed on the cell surface [38, 39]. Glycolytically and oxidatively both compartments point out the lactate production through muscle and brain cells. Likely, glycolytically and oxidatively tumor cells are high in majority and the physiological function has also observed in lactate shuttling in cancers [11]. In this study, the hypoxia tumor cells implies on a biochemical symbiosis in which both hypoxic and oxygenated tumor cells commonly stimulate their access to energy metabolites. In terms of oxidative tumor cells, cells prefers to utilize lactate in the presence of glucose as an oxidative source and recommends glycolytic cells consume the glucose for diffusion. Continuous production of reduced NADH as well as oxidation of lactate into glycolysis product (pyruvate) through LDH-1, essential process for lactate replenishing.

The high diagnostically efficacy of particular tumor symbiosis in the presence of MCT1 inhibitors is nowadays investigated with AZD3965, a compound that essential in clinical trials for advanced solid tumors. MCT4 is an alternative that could be to target lactate modulators [20]. And co-culture techniques described with analysis of human breast cancer samples also observed MCT4 presence in stromal cells whereas tumor cells was expressed in MCT1 [16].

2. Tumor Intrusion and Evolution

Accurate mechanism is provided by MCTs in which transport of each molecule of lactate with a proton as passive symporters. And glycolytic biochemical pathway is faster than ATP production through OXPHOS and as compared to OXPHOS, normally more amount of glycolysis combined to biosynthetic pathways gives high production of lactate which conveys to intracellular trafficking & death [40]. MCT4 is specifically adapted to hypoxia induced expression and a high turnover rate [41-43]. Despite MCTs, carbonic anhydrases and sodium proton exchanger used as apparatus in tumor causing cells which confirming the proton conveyance [44].

Normally, there are two forms of acids exist in tumor cells in essence carbonic acid and lactic acid. And it is necessary to point out that glycolysis gives two molecules of lactate from one molecule of glucose mainly doesn't indulge straightly to the production of protons needed for lactate conveyance. But on the other side, many sources of carbon-di-oxide might be combined with oxygen consumptions and carbon-di-oxide in the presence of carbonic anhydrases resulted out in the form of H^+ and HCO_3^- intracellular.

Hydrolysis of ATP and the lysis of nitrogen could be other source of acidity and this postulates that lactate is a causative agent of tumor acidification is responsible for interaction between increased lactic acid concentration and pH (6.7) [45,

46]. And many theories have also elaborated the contribution of tumor acidity to intrusion and evolution that has been main subject in nowadays articles [47, 48]. Extracellular acidification attends to abolition of normal tissue through caspase-mediated interaction of p53 expression [49]. One of the most important factor which under the title of acidosis to tumor progression is evolutionary facilitation and cancer cells mostly needed extracellular degradation and rebounding, a mechanism facilitated by extracellular acidification [48, 50]. Izumi et al [51] noted that MCT4 and MCT1 plays a major role in cancer cells intrusion and specially MCT1 expression certainly interacted with in vivo intrusively of human lung cancer cells and inhibitors reduced both transportation and intrusion. In another experiments, CD44 expression and hyaluronan production, transmembrane receptors by fibroblast [52] and melanoma cells [50] was observed through lactate. Lactic acid and lactate are perplexed in nature, and the lactate anion is responsible for only initiate to be characterized and based on given data, MCT inhibitors for the transportation of cancer metastasis as previously studied [53].

3. Lactate Acts as a Signaling Molecule

Sometimes lactate acts as a signaling molecule and also takes part in activate to the transcription including mitochondrial activities, transcription activation, cell maturation, apoptosis [54]. Lactate is also responsible for reactive oxygen species production certainly and modulated the DNA binding of NF- κ B & NRF-2 [54]. Lactate has been observed as a hypoxia-mimetic ability to initiate the transcription factor HIF-4 in cancer cells [55, 56]. Commonly, oxygen being a essential substrate for their activities reduced under hypoxia [57, 54]. Serving a potential rational modulating the exogenous lactate HIF-1 enterprise in normoxic tumor cells. According to previous study and unpublished data clarifies that lactate is less rapid and effective than pyruvate in inducing HIF-1 protein stabilization because pyruvate increased the transcription factors such as HIF-1 specific genes including VEGF, GLUT3, aldolase-A in Hep3G human hepatoma cells [58]. Lactate-induced HIF-1 alpha correlation was confirmed by various studies in cancer cell lines but not in Hep3G cells in which pyruvate continually induced EPO gene transcription.

Lactate was observed to increased TLR4 signaling and NF- κ B dependent gene expression in macrophages [59]. MCT inhibitors indicating that lactate is oxidized into pyruvate might play a role in which targeting or specific MCT pharmacologically could inhibit lactate signaling process. And this pathway has been better investigated in human umbilical vein endothelial cells (HUVECs). On the other hand, lactate-stimulated reactive oxygen species production was verified to initiate the degradation of the NF- κ B inhibitor through serine protein degradation. Many cases indicates that lactate might affect the other additional biochemical pathways such as lactic acid mediate the transcription and protein secretion of TGF- β 2 in initial culture of high grade glioma [60]. However, acidification may indeed play a central role in

molecular mechanism of lactate signaling provided by immunologists; lactate increase the transcription of IL-23p19 (tumor promoting IL-23, pro-inflammatory p19) in monocytes modulated with a TLR2 or TLR4 ligand. The signaling molecules and transcription pathways regulated by lactic acid

that have broad spread effects on cancer or tumor metabolism and metastasis. However, few activities of lactate have been elucidated in advance and some major insights are still expected to transmission specific therapeutic targets.

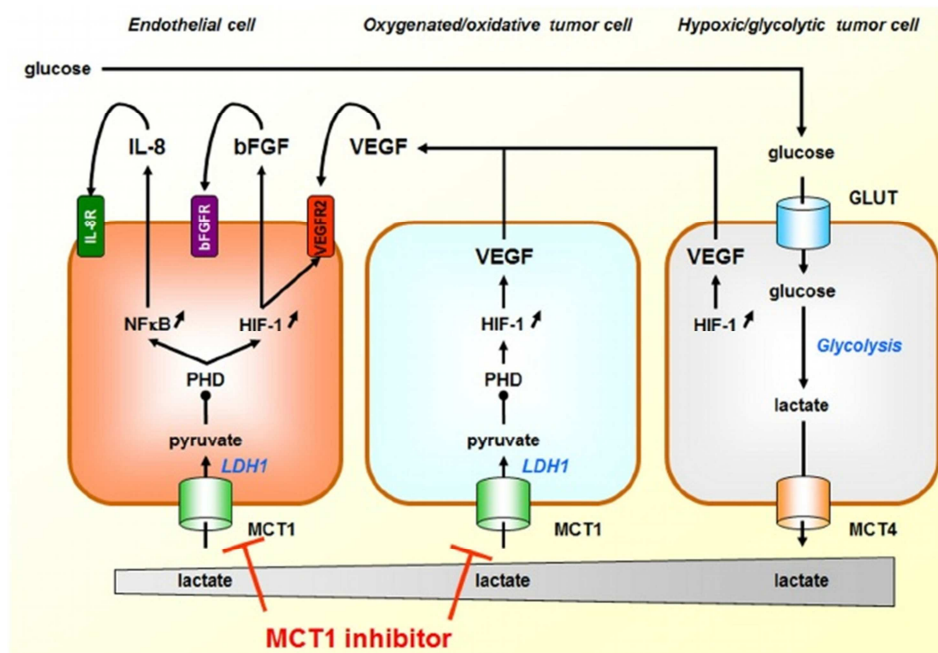


Figure 2. Lactate signaling mechanism in tumor cells.

4. Summary and Conclusion

Mostly cancer cell depends on aerobic glycolysis because cancer cells pillaging high amount of glucose from micro-environments and produce more lactic acid for energy and metabolism. Most of tumor cells activities still need to be discovered but in tumors, lactic acid is transported from glycolytic cancer cells & stromal cells. Lactate acidosis indulged the biochemical activities different from glycolysis and transport through MCTs. And lactate might strive MCT-independent activities in tumors through protons. Many biological activities of lactic acids in cancers might be specified therapeutically in the presence of MCT inhibitors and many intrinsic activities of the lactate anion remains to be characterized for therapy.

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