Science Journal of Clinical Medicine
2020; 9(1): 1-6
http://www.sciencepublishinggroup.com/j/sjcm
doi: 10.11648/j.sjcm.20200901.11
ISSN: 2327-2724 (Print); ISSN: 2327-2732 (Online)

Review Article

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

Sameer Sharma*, Rajan Chourasiya, Shahna T, Gaddam Roopa Shivani

Department of Biotechnology, Indian Academy Degree College-Autonomous, Bangalore, India

Email address:

Sameer21.97@gmail.com (S. Sharma)

*Corresponding author

To cite this article:

Sameer Sharma, Rajan Chourasiya, Shahna T, Gaddam Roopa Shivani. Role of Lactic Acid in Cancer Metabolism Under the Influences on Tumor Expansion and Metamorphosis: A Review. *Science Journal of Clinical Medicine*. Vol. 9, No. 1, 2020, pp. 1-6.
doi: 10.11648/j.sjcm.20200901.11

Received: December 24, 2019; **Accepted**: January 2, 2020; **Published**: January 10, 2020

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 1enterprise 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.

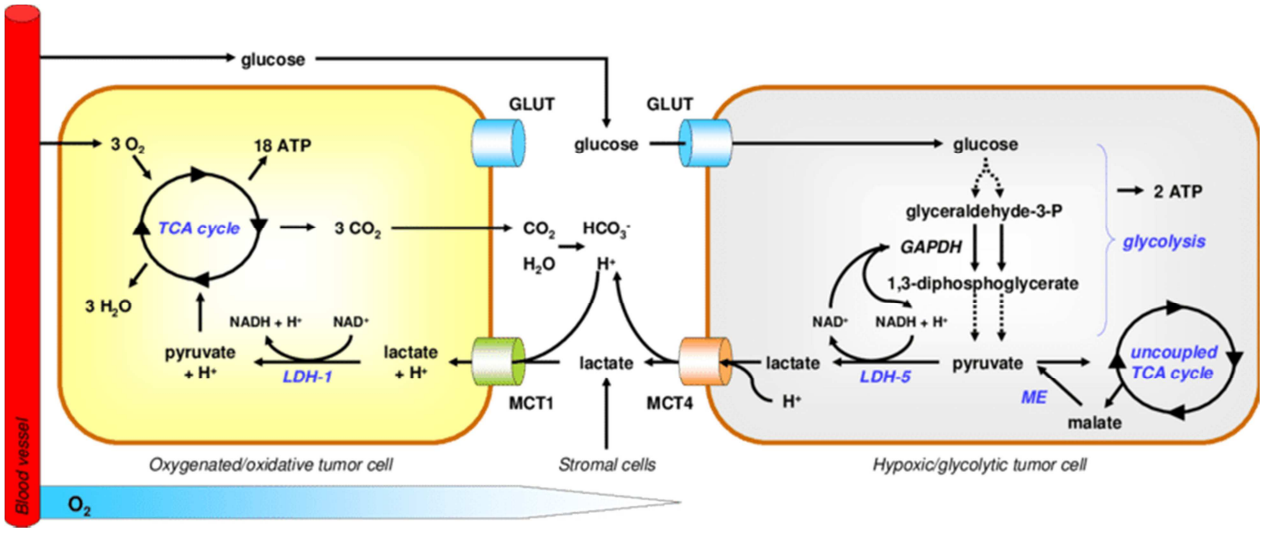

Figure 1. *Mechanism of lactate shuttles in tumors.*

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 HCO3intracellular.

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 melanomal 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-kB & 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-1protein 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 continuingly induced EPO gene transcription.

Lactate was observed to increased TLR4 signaling and NF-kB 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-kB 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-β2 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.

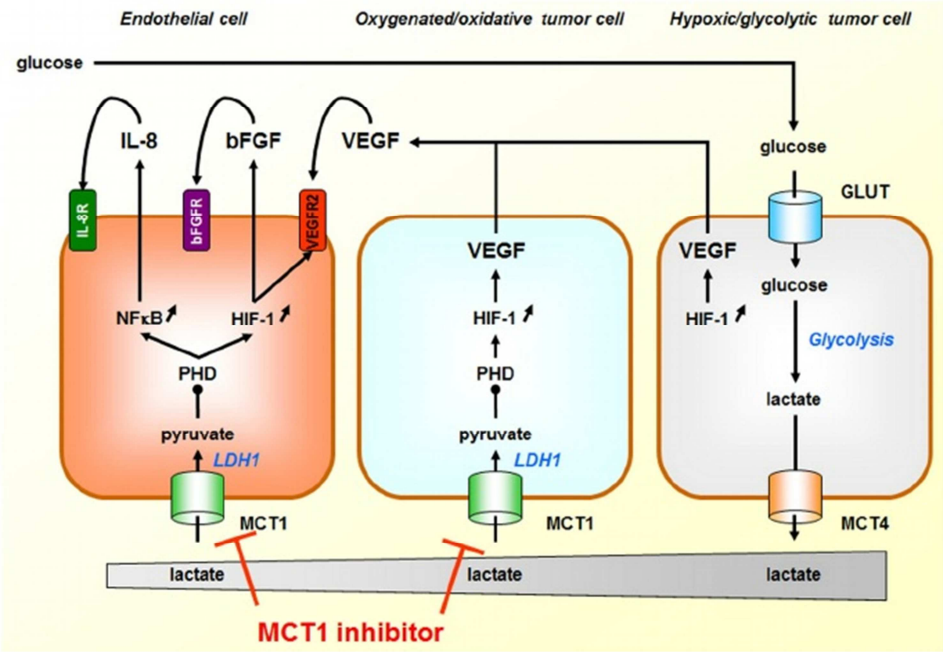

Figure 2. *Lactate signaling mechanism in tumor cells.*

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.

References

[1] Kim JW, Tchernyshyov I, Semenza GL, Dang CV. HIF-1-mediated expression of pyruvate dehydrogenase kinase: a metabolic switch required for cellular adaptation to hypoxia. Cell Metab 2006; 3: 177-85.

[2] Papandreou I, Cairns RA, Fontana L, Lim AL, Denko NC. HIF-1 mediates adaptation to hypoxia by actively downregulating mitochondrial oxygen consumption. Cell Metab 2006; 3: 187-97.

[3] DeBerardinis RJ, Mancuso A, Daikhin E, et al. Beyond aerobic glycolysis: transformed cells can engage in glutamine metabolism that exceeds the requirement for protein and nucleotide synthesis. Proc Natl Acad Sci USA 2007; 104: 19345-50.

[4] Dimmer KS, Friedrich B, Lang F, Deitmer JW, Broer S. The lowaffinity monocarboxylate transporter MCT4 is adapted to the export of lactate in highly glycolytic cells. Biochem J 2000; 350 Pt 1: 219-27.

[5] Walenta S, Mueller-Klieser WF. Lactate: mirror and motor of tumor malignancy. Semin Radiat Oncol 2004; 14: 267-74.

[6] Warburg O, Wind F, Negelein E. The metabolism of tumors in the body. J Gen Physiol 1927; 8: 519-30.

[7] Gambhir SS, Czernin J, Schwimmer J, Silverman DH, Coleman RE, Phelps ME. A tabulated summary of the FDG PET literature. J Nucl Med 2001; 42: 1S-93S.

[8] Kelloff GJ, Hoffman JM, Johnson B, et al. Progress and promise of FDG-PET imaging for cancer patient management and oncologic drug development. Clin Cancer Res 2005; 11: 2785-808.

[9] Gladden LB. Lactate metabolism: a new paradigm for the third millennium. J Physiol 2004; 558: 5-30.

[10] Cori CF, Cori GT. Glycogen formation in the liver with d- and llactic acid. J Biol Chem 1929; 81: 389-403.

[11] Sonveaux P, Vegran F, Schroeder T, et al. Targeting lactate-fueled respiration selectively kills hypoxic tumor cells in mice. J Clin Invest 2008; 118: 3930-42.

[12] Semenza GL. Tumor metabolism: cancer cells give and take lactate. J Clin Invest 2008; 118: 3835-7.

[13] Feron O. Pyruvate into lactate and back: from the Warburg effect to symbiotic energy fuel exchange in cancer cells. Radiother Oncol 2009; 92: 329-33.

[14] Bonuccelli G, Tsirigos A, Whitaker-Menezes D, et al. Ketones and lactate "fuel" tumor growth and metastasis: Evidence that epithelial cancer cells use oxidative mitochondrial metabolism. Cell Cycle 2010; 9: 3506-14.

[15] Martinez-Outschoorn UE, Pavlides S, Howell A, et al. Stromalepithelial metabolic coupling in cancer: Integrating autophagy and metabolism in the tumor microenvironment. Int J Biochem Cell Biol 2011; 43: 1045-51.

[16] Whitaker-Menezes D, Martinez-Outschoorn UE, Lin Z, et al. Evidence for a stromal-epithelial "lactate shuttle" in human tumors: MCT4 is a marker of oxidative stress in cancer-associated fibroblasts. Cell Cycle 2011; 10: 1772-83.

[17] Lu H, Forbes RA, Verma A. Hypoxia-inducible factor 1 activation by aerobic glycolysis implicates the Warburg effect in carcinogenesis. J Biol Chem 2002; 277: 23111-5.

[18] Lu H, Dalgard CL, Mohyeldin A, McFate T, Tait AS, Verma A. Reversible inactivation of HIF-1 prolyl hydroxylases allows cell metabolism to control basal HIF-1. J Biol Chem 2005; 280: 41928-39.

[19] Vegran F, Boidot R, Michiels C, Sonveaux P, Feron O. Lactate influx through the endothelial cell monocarboxylate transporter MCT1 supports an NF-kappaB/IL-8 pathway that drives tumor angiogenesis. Cancer Res 2011; 71: 2550-60.

[20] Gallagher SM, Castorino JJ, Wang D, Philp NJ. Monocarboxylate transporter 4 regulates maturation and trafficking of CD147 to the plasma membrane in the metastatic breast cancer cell line MDAMB-231. Cancer Res 2007; 67: 4182-9.

[21] Deora AA, Philp N, Hu J, Bok D, Rodriguez-Boulan E. Mechanisms regulating tissue-specific polarity of monocarboxylate transporters and their chaperone CD147 in kidney and retinal epithelia. Proc Natl Acad Sci USA 2005; 102: 16245-50

[22] Slomiany MG, Grass GD, Robertson AD, et al. Hyaluronan, CD44, and emmprin regulate lactate efflux and membrane localization of monocarboxylate transporters in human breast carcinoma cells. Cancer Res 2009; 69: 1293-301.

[23] Ellis SM, Nabeshima K, Biswas C. Monoclonal antibody preparation and purification of a tumor cell collagenase-stimulatory factor. Cancer Res 1989; 49: 3385-91.

[24] Ishibashi Y, Matsumoto T, Niwa M, et al. CD147 and matrix metalloproteinase-2 protein expression as significant prognostic factors in esophageal squamous cell carcinoma. Cancer 2004; 101: 1994-2000.

[25] Ueda K, Yamada K, Urashima M, et al. Association of extracellular matrix metalloproteinase inducer in endometrial carcinoma with patient outcomes and clinicopathogenesis using monoclonal antibody 12C3. Oncol Rep 2007; 17: 731-5.

[26] Biswas C, Zhang Y, DeCastro R, et al. The human tumor cellderived collagenase stimulatory factor (renamed EMMPRIN) is a member of the immunoglobulin superfamily. Cancer Res 1995; 55: 434-9.

[27] Kanekura T, Chen X, Kanzaki T. Basigin (CD147) is expressed on melanoma cells and induces tumor cell invasion by stimulating production of matrix metalloproteinases by fibroblasts. Int J Cancer 2002; 99: 520-8.

[28] Chen X, Lin J, Kanekura T, et al. A small interfering CD147-targeting RNA inhibited the proliferation, invasiveness, and metastatic activity of malignant melanoma. Cancer Res 2006; 66: 11323- 30.

[29] Miyauchi S, Gopal E, Fei YJ, Ganapathy V. Functional identification of SLC5A8, a tumor suppressor down-regulated in colon cancer, as a Na(+)-coupled transporter for short-chain fatty acids. J Biol Chem 2004; 279: 13293-6.

[30] Gopal E, Fei YJ, Sugawara M, et al. Expression of slc5a8 in kidney and its role in Na(+)-coupled transport of lactate. J Biol Chem 2004; 279: 44522-32.

[31] Ganapathy V, Thangaraju M, Gopal E, et al. Sodium-coupled monocarboxylate transporters in normal tissues and in cancer. AAPS J 2008; 10: 193-9.

[32] Li H, Myeroff L, Smiraglia D, et al. SLC5A8, a sodium transporter, is a tumor suppressor gene silenced by methylation in human colon aberrant crypt foci and cancers. Proc Natl Acad Sci USA 2003; 100: 8412-7.

[33] Bonen A. The expression of lactate transporters (MCT1 and MCT4) in heart and muscle. Eur J Appl Physiol 2001; 86: 6-11.

[34] McCullagh KJ, Poole RC, Halestrap AP, O'Brien M, Bonen A. Role of the lactate transporter (MCT1) in skeletal muscles. Am J Physiol 1996; 271: E143-50.

[35] Bonen A, McCullagh KJ, Putman CT, Hultman E, Jones NL, Heigenhauser GJ. Short-term training increases human muscle MCT1 and femoral venous lactate in relation to muscle lactate. Am J Physiol 1998; 274: E102-7.

[36] Bouzier-Sore AK, Voisin P, Canioni P, Magistretti PJ, Pellerin L. Lactate is a preferential oxidative energy substrate over glucose for neurons in culture. J Cereb Blood Flow Metab 2003; 23: 1298-306.

[37] Pellerin L, Magistretti PJ. Neuroenergetics: calling upon astrocytes to satisfy hungry neurons. Neuroscientist 2004; 10: 53-62.

[38] Pellerin L, Bergersen LH, Halestrap AP, Pierre K. Cellular and subcellular distribution of monocarboxylate transporters in cultured brain cells and in the adult brain. J Neurosci Res 2005; 79: 55-64.

[39] Halestrap AP, Meredith D. The SLC16 gene family-from monocarboxylate transporters (MCTs) to aromatic amino acid transporters and beyond. Pflugers Arch 2004; 447: 619-28.

[40] Curi R, Newsholme P, Newsholme EA. Metabolism of pyruvate by isolated rat mesenteric lymphocytes, lymphocyte mitochondria and isolated mouse macrophages. Biochem J 1988; 250: 383-8.

[41] Chiche J, Fur YL, Vilmen C, et al. In vivo pH in metabolicdefective Ras-transformed fibroblast tumors: Key role of the monocarboxylate transporter, MCT4, for inducing an alkaline intracellular pH. Int J Cancer 2011.

[42] Ullah MS, Davies AJ, Halestrap AP. The plasma membrane lactate transporter MCT4, but not MCT1, is up-regulated by hypoxia through a HIF-1alpha-dependent mechanism. J Biol Chem 2006; 281: 9030-7.

[43] Porporato PE, Dadhich RK, Dhup S, Copetti T, Sonveaux P. Anticancer targets in the glycolytic metabolism of tumors: a comprehensive review. Front Pharmacol 2011; 2: 49.

[44] Newell K, Franchi A, Pouyssegur J, Tannock I. Studies with glycolysis-deficient cells suggest that production of lactic acid is not the only cause of tumor acidity. Proc Natl Acad Sci USA 1993; 90: 1127-31.

[45] Yamagata M, Hasuda K, Stamato T, Tannock IF. The contribution of lactic acid to acidification of tumours: studies of variant cells lacking lactate dehydrogenase. Br J Cancer 1998; 77: 1726-31.

[46] Cardone RA, Casavola V, Reshkin SJ. The role of disturbed pH dynamics and the Na+/H+ exchanger in metastasis. Nat Rev Cancer 2005; 5: 786-95.

[47] Gatenby RA, Gawlinski ET, Gmitro AF, Kaylor B, Gillies RJ. Acid-mediated tumor invasion: a multidisciplinary study. Cancer Res 2006; 66: 5216-23.

[48] Williams AC, Collard TJ, Paraskeva C. An acidic environment leads to p53 dependent induction of apoptosis in human adenoma and carcinoma cell lines: implications for clonal selection during colorectal carcinogenesis. Oncogene 1999; 18: 3199-204.

[49] Smallbone K, Gatenby RA, Gillies RJ, Maini PK, Gavaghan DJ. Metabolic changes during carcinogenesis: potential impact on invasiveness. J Theor Biol 2007; 244: 703-13.

[50] Izumi H, Takahashi M, Uramoto H, et al. Monocarboxylate transporters 1 and 4 are involved in the invasion activity of human lung cancer cells. Cancer Sci 2011; 102: 1007-13.

[51] Stern R, Shuster S, Neudecker BA, Formby B. Lactate stimulates fibroblast expression of hyaluronan and CD44: the Warburg effect revisited. Exp Cell Res 2002; 276: 24-31.

[52] Rudrabhatla SR, Mahaffey CL, Mummert ME. Tumor microenvironment modulates hyaluronan expression: the lactate effect. J Invest Dermatol 2006; 126: 1378-87.

[53] Hashimoto T, Hussien R, Oommen S, Gohil K, Brooks GA. Lactate sensitive transcription factor network in L6 cells: activation of MCT1 and mitochondrial biogenesis. FASEB J 2007; 21: 2602-12.

[54] Hirsila M, Koivunen P, Gunzler V, Kivirikko KI, Myllyharju J. Characterization of the human prolyl 4-hydroxylases that modify the hypoxia-inducible factor. J Biol Chem 2003; 278: 30772-80.

[55] Pugh CW, Ratcliffe PJ. Regulation of angiogenesis by hypoxia: role of the HIF system. Nat Med 2003; 9: 677-84.

[56] Samuvel DJ, Sundararaj KP, Nareika A, Lopes-Virella MF, Huang Y. Lactate boosts TLR4 signaling and NF-kappaB pathwaymediated gene transcription in macrophages via monocarboxylate transporters and MD-2 up-regulation. J Immunol 2009; 182: 2476-84.

[57] Baumann F, Leukel P, Doerfelt A, et al. Lactate promotes glioma migration by TGF-beta2-dependent regulation of matrix metalloproteinase-2. Neuro Oncol 2009; 11: 368-80.

[58] Shime H, Yabu M, Akazawa T, et al. Tumor-secreted lactic acid promotes IL-23/IL-17 proinflammatory pathway. J Immunol 2008; 180: 7175-83.