



Lactate as a key metabolic intermediate in cancer

L. Bruce Gladden

School of Kinesiology, Auburn University, Auburn, AL, USA

Correspondence to: L. Bruce Gladden. School of Kinesiology, Auburn University, 301 Wire Road, Auburn, AL 36849, USA. Email: gladdlb@auburn.edu.

Provenance: This is an invited article commissioned by the Editors in Chief Prof. Dr. Xuehao Wang, Prof. Dr. Jianxing He, and Prof. Dr. Rafael Rosell [Academician of the Chinese Academy of Engineering, Director of the Institute of Liver Surgery, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China; Department of Cardiothoracic Surgery, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, Guangdong, China; Cancer Biology and Precision Medicine Program, Catalan Institute of Oncology, Hospital Germans Trias i Pujol, Ctra Canyet, Badalona (Barcelona), Spain].

Comment on: Goodwin ML, Pennington Z, Westbrook EM, *et al.* Lactate and cancer: a “lactatic” perspective on spinal tumor metabolism (part 1). *Ann Transl Med* 2019;7:220.

Submitted Jan 17, 2019. Accepted for publication Jan 24, 2019.

doi: 10.21037/atm.2019.01.60

View this article at: <http://dx.doi.org/10.21037/atm.2019.01.60>

In 1985, George Brooks proposed the “Lactate Shuttle” (1), subsequently labeled the “Cell-Cell Lactate Shuttle” (2-4). In that initial treatise, relying largely on the use of isotopic tracers, he proposed a new concept for lactate (La^-) as a central player in metabolism during both rest and exercise. He proposed the passage of much of glycolytic and gluconeogenic flux through the La^- pool at rates which were quantitatively as important as glucose flux. This scheme of La^- as a key metabolic intermediate was a dramatic departure from previous thinking which viewed La^- simply as a dead-end, fatigue-causing metabolite that was largely the result of muscle hypoxia during exercise (1,4-6). In this current special issue of *Annals of Translational Medicine*, focused on spinal tumor surgery, Goodwin *et al.* (7) provide a compelling introduction into this currently accepted theory of whole body La^- metabolism and then address cancer metabolism in the context of this modern understanding of the metabolic role of La^- .

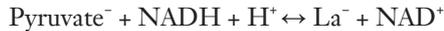
Despite the foresight of his lactate shuttle theory, and prior classic work in the 1920's, Brooks did not envision the potential for a tumor lactate shuttle at that time, an idea that is most clearly described by Semenza (8) on the basis of classic work by Sonveaux *et al.* (9). The key relevance of La^- metabolism in cancer was presaged by the research of Otto Warburg [described in (10)] and the Cori's (11) as clearly described by Goodwin *et al.* (7) and Pennington *et al.* (12) in this issue of the journal. In general, cancer cells live in an ocean of glucose and many of them are

primary La^- producers that generate La^- concentrations which may be 40 times greater than that found in normal resting cells (13); a characteristic that is correlated with cancer aggressiveness (13,14). Cancer cells that are rapid La^- producers even in the presence of a sufficient O_2 supply are called Warburg cells (15,16). However, this is an overly simplistic view of tumor La^- metabolism. In reality, tumors may contain Warburg cells, reverse Warburg cells (cells that readily consume La^- as a fuel), and a variety of supporting cells including immune cells, non-cancer stromal cells, fibroblasts, endothelial cells and lymphatics (3,17). This composition likely varies with different cancer types and over time within a given tumor mass.

This structural and temporal variety of cell subtypes within a tumor mass calls for further study of the phenotypic metabolic profiles of cells within different types of cancers at different stages of growth. Such a profile would include fuel preference (e.g., glucose *vs.* La^-), mitochondrial function via respirometry, capillarity, intracellular and extracellular pH, and PO_2 . Further key measures would include oxidative enzyme activities, glycolytic enzyme activities, and ideally, analysis of key controllers of the glycolytic pathway as elegantly researched by the Rabinowitz group (18). Obviously, such characterization would entail research both *in vivo-in situ* [e.g., MRI as in (14)] and *in vitro* [e.g., (9)].

La^- shuttling implicitly involves several key functions such as production, transport, and removal. Two important components that have received much attention are the

isoform types of lactate dehydrogenase (LDH) and the monocarboxylate transporters that facilitate La^- diffusion as noted by Goodwin *et al.* (7) and Pennington *et al.* (12). LDH catalyzes the formation of La^- as illustrated below:



LDH was the first enzyme for which isoforms/isozymes were discovered (19). Each isozyme is a tetramer with each of the four monomers being either an H subunit (for heart) or an M subunit (for muscle). This leads to five combinations as follows: H_4 , H_3M_1 , H_2M_2 , H_1M_3 , and M_4 . The modern terminology designates the monomers as A (muscle) and B (heart) and the cancer literature usually discusses LDHA *vs.* LDHB (7). Intriguingly, there is a strong correlation between the expression of LDHA and a tissue phenotype (e.g., many cancer cells and type II fast twitch glycolytic muscle fibers) that has a tendency to produce La^- (4,7,13,19,20). This has led to the prevailing, erroneous view that these LDH isozyme profiles are causative in terms of lactate production versus consumption (20,21). Of prime emphasis is the fact that enzymes do not change the essential characteristics of chemical reactions; they only change the rate at which the equilibrium is reached (21). In the case of LDH, in most tissues its activity appears to be high relative to that of other enzymes in the glycolytic pathway or enzymes in the oxidative pathway (20). Additionally, the differences in maximal reaction rate (V_{max}), substrate affinity (K_m), and inhibitory responses to pyruvate between the LDHA and LDHB are insufficiently convincing (19-21) of a causative role in behavior of the overall reaction. In terms of application to cancer, it may be that experiments showing positive effects with LDHA knockdown [see (12) for review] are achieving those results simply because total LDH activity is being impacted. LDH isozymes, then, present a conundrum. On the one hand, their correlative distribution relative to tissue glycolytic and oxidative phenotypes imply some sort of important role; what was the selective trait driving their existence? On the other hand, thermodynamics of the overall reaction, and the function of the LDH isozymes do not reveal evidence of causation. My conclusion is that we still need to learn the exact role, if any, of the LDH isozymes; this requires additional experimentation, including modeling studies *in silico*. Despite these knowledge gaps, LDH inhibition remains a potentially productive target for investigation of cancer treatment (7,12).

The monocarboxylate transporters (MCTs) present a similar enigma to that of the LDH isozymes. The MCTs are

a family of 14 related proteins with only four (MCTs 1-4) known to be important in the transport of La^- , pyruvate, and ketone bodies (4,13). La^- is facilitated in diffusion down its concentration gradient by MCTs, apparently in co-transport with a hydrogen ion (H^+), greatly speeding the La^- transmembrane flux rate beyond that of simple diffusion. An $[\text{H}^+]$ gradient enhances La^- transfer in the direction of low pH to high pH, apparently due to the cotransport of the two ions by the MCTs. Similarly, to the case for LDH isozymes, there is a correlative expression pattern for the MCTs in that MCT1 expression is highly correlated with indices of oxidative metabolism while MCT4 expression tends to coincide with indices of glycolytic metabolism (3,4,13). The relevance of this distribution is unclear given that MCT4, which is typically found to a greater extent in La^- -producing tumors and fast glycolytic muscle fibers (3,4,13), has Michaelis-Menten characteristics that might more likely lead to an intracellular retention of La^- in comparison to the characteristics of MCT1, which is more often located in oxidative tissues. Additionally, oxidative muscle cells with a preponderance of MCT1 tend to have a much greater V_{max} for La^- transport than do glycolytic muscle cells which have a greater MCT4 content (4). Again, a better understanding of basic function is needed, but in the meantime MCTs remain a useful target for cancer intervention (3,9,13,22).

Pennington, Goodwin *et al.* (13) in this issue have emphasized the putative role of a low pH in the extracellular tumor environment as a promoting element in tumor growth and metastasis. Many cancer cells are unique in that, unlike most normal cells, they have a lower extracellular pH (pH_e) in comparison to intracellular pH (pH_i) (14,23). As a result and again unlike most normal cells, $[\text{La}^-]$ inside tumor cells tends to be two or more times higher than the tumor extracellular $[\text{La}^-]$ (23). For normal cell types, La^- is distributed in the opposite direction of H^+ . This low extracellular pH_e in tumors presents a hostile environment to surrounding tissue and is conducive to infiltration, tumor growth and metastasis (14) while the alkaline pH_i promotes cell proliferation (23). Clearly, additional pH regulating proteins are involved since La^- , which is a causative agent in acidosis via its role as a strong ion, is higher inside the cancer cell where pH is higher and lower in the extracellular environment where pH is lower (23). As a result, research is underway to alter the tumor environment and to target pH regulators (23).

In closing, a couple of additional comments are important. First, it has been suggested that from a genotypic

viewpoint, there may be hundreds or thousands of unique cancers, but a much smaller number of cancer *phenotypes* (17). This argues strongly for continued and increasing emphasis on research into the tumor metabolism phenotype. Second, Goodwin *et al.* (7) make a robust and convincing case for increased cancer research on large animal models with naturally occurring cancers. Cellular research *in vitro* is certainly valuable, but falls short in attempts to replicate the tumor microenvironment. For example, cell cultures are usually hyperglycemic and hyperoxic relative to conditions *in vivo* and do not contain the variety of cells that constitute tumors. While genetic manipulations may be easier in mouse and cell models, large animal models are a step closer to humans and are far superior for phenotypic studies. Research leading to understanding of metabolism and bioenergetics has received fewer and lesser accolades than those showered on advancements in evolution, genetics, and molecular biology (4). Perhaps we are finally arriving at a time when metabolism will take center stage.

Acknowledgments

None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

References

- Brooks GA. Lactate: Glycolytic end product and oxidative substrate during sustained exercise in mammals – The “Lactate Shuttle”. In: Gilles R (ed) Circulation, respiration, and metabolism: current comparative approaches. Available online: https://doi.org/10.1007/978-3-642-70610-3_15
- Brooks GA. Cell-cell and intracellular lactate shuttles. *J Physiol* 2009;587:5591-600.
- Brooks GA. The Science and Translation of Lactate Shuttle Theory. *Cell Metab* 2018;27:757-85.
- Ferguson BS, Rogatzki MJ, Goodwin ML, et al. Lactate metabolism: historical context, prior misinterpretations, and current understanding. *Eur J Appl Physiol* 2018;118:691-728.
- Fletcher WM, Hopkins FG. Lactic acid in amphibian muscle. *J Physiol* 1907;35:247-309.
- Wasserman K, Whipp BJ, Koyle SN, et al. Anaerobic threshold and respiratory gas exchange during exercise. *J Appl Physiol* 1973;35:236-43.
- Goodwin ML, Pennington Z, Westbrook EM, et al. Lactate and cancer: a “lactatic” perspective on spinal tumor metabolism (part 1). *Ann Transl Med* 2019;7:220.
- Semenza GL. Tumor metabolism: cancer cells give and take lactate. *J Clin Invest* 2008;118:3835-7.
- Sonveaux P, Végran F, Schroeder T, et al. Targeting lactate-fueled respiration selectively kills hypoxic tumor cells in mice. *J Clin Invest* 2008;118:3930-42.
- Vander Heiden MG, Cantley LC, Thompson CB. Understanding the Warburg effect: the metabolic requirements of cell proliferation. *Science* 2009;324:1029-33.
- Cori CF, Cori GT. The carbohydrate metabolism of tumors: II. Changes in the sugar, lactic acid, and CO₂-combining power of blood passing through a tumor. *J Biol Chem* 1925;65:397-405.
- Pennington Z, Goodwin ML, Westbrook EM, et al. Lactate and cancer: spinal metastases and potential therapeutic targets (part 2). *Ann Transl Med* 2019;7:221.
- San-Millán I, Brooks GA. Reexamining cancer metabolism: lactate production for carcinogenesis could be the purpose and explanation of the Warburg Effect. *Carcinogenesis* 2017;38:119-33.
- Gillies RJ, Raghunand N, Karczmar GS, et al. MRI of the tumor microenvironment. *J Magn Reson Imaging* 2002;16:430-50.
- Racker E. Bioenergetics and the problem of tumor growth. *Am Sci* 1972;60:56-63.
- Goodwin ML, Gladden LB, Nijsten MW, Jones KB. Lactate and cancer: revisiting the warburg effect in an era of lactate shuttling. *Front Nutr* 2015;1:27.
- Gladden LB, Goodwin ML, McDonald JR, et al. Fuel for cancer cells? *Cell Cycle* 2011;10:2421-2.
- Tanner LB, Goglia AG, Wei MH, et al. Four Key Steps Control Glycolytic Flux in Mammalian Cells. *Cell Syst* 2018;7:49-62.e8.
- Gladden LB. 200th anniversary of lactate research in muscle. *Exerc Sport Sci Rev* 2008;36:109-15.
- Rogatzki MJ, Ferguson BS, Goodwin ML, et al. Lactate is always the end product of glycolysis. *Front Neurosci* 2015;9:22.
- Bak LK, Schousboe A. Misconceptions regarding basic thermodynamics and enzyme kinetics have led to erroneous conclusions regarding the metabolic importance of lactate dehydrogenase isoenzyme expression. *J Neurosci Res* 2017;95:2098-102.

22. Parks SK, Pouysségur J. Targeting pH regulating proteins for cancer therapy-Progress and limitations. *Semin Cancer Biol* 2017;43:66-73.
23. Stubbs M, McSheehy PM, Griffiths JR, et al. Causes and consequences of tumour acidity and implications for treatment. *Mol Med Today* 2000;6:15-9.

Cite this article as: Gladden LB. Lactate as a key metabolic intermediate in cancer. *Ann Transl Med* 2019;7(10):210. doi: 10.21037/atm.2019.01.60