Journal of
Cancer Science & Therapy

Ganapathy-Kanniappan, J Cancer Sci Ther 2016, 8:2
DOI: 10.4172/1948-5956.1000385

Short Communication Open Access

Selective Inhibition of Lactate Influx in Cancer: An Opportunity to Augment Therapeutic Targeting

Shanmugasundaram Ganapathy-Kanniappan*

Department of Radiology and Radiological Sciences, The Johns Hopkins University School of Medicine, Baltimore, MD, USA

Short Communication

I read with great interest the article by Draoui et al., on a new class of inhibitors of lactate influx in cancer [1]. The authors report characterization of a novel compound, 7-amino carboxycoumarin (7-ACC), which specifically inhibits one of the members of monocarboxylate transporters (MCTs), the MCT-1. Using the substrate mimetic, an analog of pyruvate, the authors also demonstrate that 7-ACC selectively blocks lactate-influx and does not interfere with the uptake of the mimetic thus establishing the molecular specificity of 7-ACC in the inhibition of lactate uptake.

Recently, targeting "tumor glycolysis" or 'aerobic glycolysis" (i.e. the process of conversion of glucose into pyruvate followed by lactate production despite oxygen availability) using energy blockers has gained renewed interest. This is primarily due to the tremendous progress in our understanding of cancer metabolism and its clinical relevance [2]. Although the glycolytic of cancers have long been known, emerging reports indicate that cancer cells exhibit metabolic plasticity [3,4]. In other words, it is increasingly evident that cancer cells possess the capacity to switch to oxidative phosphorylation (OxPhos) if required, in the presence of oxygen and functionally active mitochondria. Biochemically, it implies that cancer cells may oxidize glucose into lactate (via glycolysis) or metabolize it through OxPhos pathway as may be necessary. Noteworthy, the product of tumor glycolysis (i.e.) lactate is exported via specific transporters called MCTs (which enables cancer cells to avoid intracellular acidification. Among MCTs, MCT-1 and MCT-4 have been investigated in detail due to their abundance as well as functional significance in lactate shuttle. In brief, MCT-1 imports lactate or pyruvate whereas MCT-4 exports lactate into the extracellular environment [5]. Functionally, over expression of MCT-1 enables cancer cells to import lactate from the extracellular environment (tumor microenvironment) for further utilization via acetyl CoA-pathway or mitochondrial metabolism. More importantly, the import of lactate provides cancer cells to alleviate excessive acidification of microenvironment [6]. Thus, MCT-1 as a lactate importer is indispensable for cancer cells to prevent lactate accumulation in tumor microenvironment. As MCTs play a pivotal role in cancer metabolism and survival, several researchers contemplated therapeutic targeting of cancer by specific MCT inhibitors. Despite encouraging results from the preclinical studies, the progress of MCT inhibitors for clinical use remains challenged, perhaps due to lack of specificity or systemic toxicity.

Since MCTs over-expression is ubiquitous in cancer, with few exceptions, the rationale to employ any anticancer therapeutic that relies on MCTs for intracellular targeting is not only feasible but also desirable. Thus, there is a growing interest in the use of small molecule inhibitors that rely on MCTs for intracellular targeting, and has been envisaged as potential anticancer strategy [7-9]. The impetus for the interest to exploit MCT-1 emanates from the biochemical phenotype of majority of cancers which show an up-regulation of MCT-1 [5]. However, one of the primary challenges for any MCT-1-dependent delivery of potential antineoplastic agent is to effectively compete with lactate (from tumor microenvironment). Such a competition with the endogenous substrate (e.g. lactate) will in turn necessitate the use of a higher dose of potential therapeutic to overcome lactate competition. Consequently, this dose-escalation has the propensity to instigate undesirable effects like systemic toxicity. In this context, if the lactate uptake is specifically blocked or markedly reduced (e.g. by 7-ACC) it would likely facilitate an increase in the cellular uptake of MCT-1-dependent anticancer agents leading to a favorable therapeutic outcome.

Intriguingly, the authors observed that despite the combinatorial approach (7-ACC and the pyruvate mimetic) the anticancer effect was similar to monotherapy (without 7-ACC) as evident by tumor size [mean (n=8)]. It is plausible that for monotherapy a maximum therapeutic dose of the mimetic was used which irrespective of the abrogation of lactate influx could promote antitumor effects. Future investigations to harness the benefits of specific inhibition of lactate influx, could use minimal therapeutic dose of potential anticancer agent (which in turn will reduce systemic toxicity) and compare between monotherapy and combinatorial approach to assess therapeutic outcome.

In cancer cells, the functional significance of MCT-4 in lactate export has long been recognized since intracellular accumulation of lactate leads to chronic acidification and cell death. However, only recently the MCT-1 dependent lactate influx has been identified as pivotal for the maintenance of tumor due to the existence of a symbiotic relationship between hypoxic and normoxic cancer cells [10]. Thus a combinatorial strategy involving the delivery of an antiglycolytic agent and an inhibitor of lactate-influx could be effective in targeting tumor energy metabolism. Although the effectiveness of this combination therapy will be relevant to cancer cells that express MCT-1, it is noteworthy that majority of tumor types have been known to up-regulate MCTs [11] suggesting that MCT-1 dependent tumor targeting in combination with specific inhibitors of lactate-influx in such malignancies could be a viable therapeutic strategy.

References

1. Draoui N, Schicke O, Seront E, Bouzin C, Sonveaux P, et al. (2014) Antitumor activity of 7-aminocarboxycoumarin derivatives, a new class of potent inhibitors of lactate influx but not efflux. Mol Cancer Ther 13: 1410-1418.

***Corresponding author:** Ganapathy-Kanniappan S, Department of Radiology & Radiological Sciences, Johns Hopkins University School of Medicine, 600 North Wolfe Street, Blalock 340, Baltimore, MD 21287, USA, Tel: + 410-502-6228; E-mail: gshanmu1@jhmi.edu

Received January 02, 2016; **Accepted** February 15, 2016; **Published** February 17, 2016

Citation: Ganapathy-Kanniappan S (2016) Selective Inhibition of Lactate Influx in Cancer: An Opportunity to Augment Therapeutic Targeting. J Cancer Sci Ther 8: 036-037. doi:10.4172/1948-5956.1000385

2. Vander Heiden MG (2011) Targeting cancer metabolism: A therapeutic window opens. Nat Rev Drug Discov 10: 671-684.

3. Fantin VR, St-Pierre J, Leder P (2006) Attenuation of LDH-A expression uncovers a link between glycolysis, mitochondrial physiology, and tumor maintenance. Cancer Cell 9: 425-434.

4. Lu CL, Qin L, Liu HC, Candas D, Fan M, et al. (2015) Tumor cells switch to mitochondrial oxidative phosphorylation under radiation via mTOR-mediated hexokinase II inhibition--a warburg-reversing effect. PLoS One 10: e0121046.

5. Draoui N, Feron O (2011) Lactate shuttles at a glance: From physiological paradigms to anti-cancer treatments. Dis Model Mech 4: 727-732.

6. Semenza GL (2008) Tumor metabolism: Cancer cells give and take lactate. J Clin Invest 118: 3835-3837.

7. Birsoy K, Wang T, Possemato R, Yilmaz OH, Koch CE, et al. (2013) MCT1-mediated transport of a toxic molecule is an effective strategy for targeting glycolytic tumors. Nat Genet 45: 104-108.

8. Ganapathy-Kanniappan S, Kunjithapatham R, Torbenson MS, Rao PP, Carson KA, et al. (2012) Human hepatocellular carcinoma in a mouse model: Assessment of tumor response to percutaneous ablation by using glyceraldehyde-3-phosphate dehydrogenase antagonists. Radiology 262: 834-845.

9. Ganapathy-Kanniappan S, Geschwind JF (2013) Tumor glycolysis as a target for cancer therapy: Progress and prospects. Mol Cancer 12: 152.

10. Sonveaux P, Vegran F, Schroeder T, Wergin MC, Verrax J, et al. (2008) Targeting lactate-fueled respiration selectively kills hypoxic tumor cells in mice. J Clin Invest 118: 3930-3942.

11. Pinheiro C, Longatto-Filho A, Azevedo-Silva J, Casal M, Schmitt FC, et al. (2012) Role of monocarboxylate transporters in human cancers: State of the art. J Bioenerg Biomembr 44: 127-139.