

# We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

185,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index  
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?  
Contact [book.department@intechopen.com](mailto:book.department@intechopen.com)

Numbers displayed above are based on latest data collected.  
For more information visit [www.intechopen.com](http://www.intechopen.com)



---

# Role of Glutamate Dehydrogenase in Cancer Growth and Homeostasis

---

Ellen Friday, Robert Oliver III, Francesco Turturro and Tomas Welbourne

Additional information is available at the end of the chapter

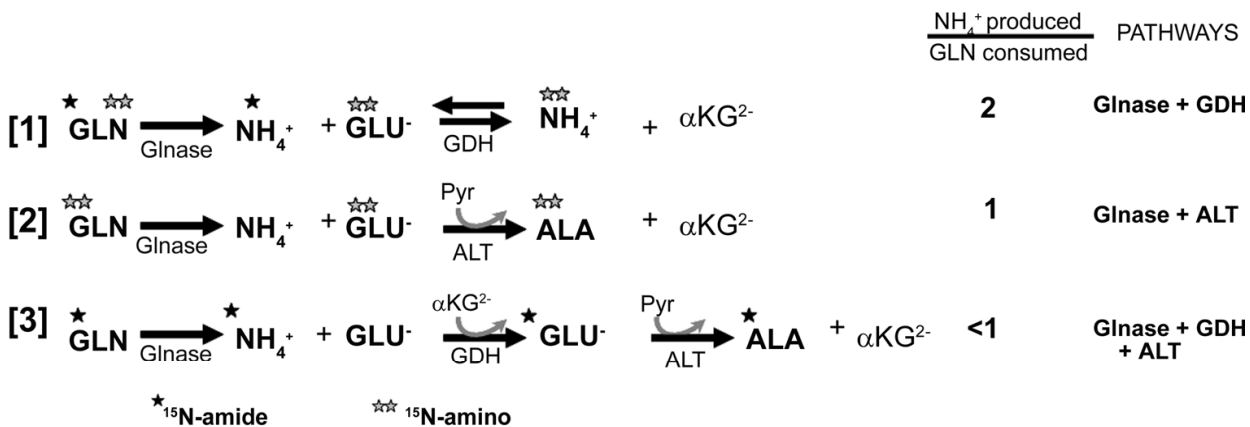
<http://dx.doi.org/10.5772/48606>

---

## 1. Introduction

Glutamate Dehydrogenase (GDH) catalyzes the oxidative conversion of glutamate to alpha ketoglutarate and ammonium supplying the TCA cycle with intermediates in support of anaplerosis (**Figure 1 Rxn1**). Conversely GDH catalyzes the reductive amination of alpha ketoglutarate and ammonium producing glutamate when the TCA cycle pool is filled. The net GDH flux resulting from these bidirectional fluxes can be obtained from the conversion of either  $^{15}\text{N}$  labeled glutamate and analyzing  $^{15}\text{N}$  ammonium or from  $^{15}\text{N}$  labeled  $\text{NH}_4^+$  and monitoring  $^{15}\text{N}$  labeled glutamate. Besides deamination and  $^{15}\text{N}$   $\text{NH}_4^+$  production,  $^{15}\text{N}$  labeled glutamate can be converted to  $^{15}\text{N}$  labeled amino acids, most prominently alanine, via transamination reactions (**Figure 1, Rxn2**). In contrast to glutamate deamination which yields net keto acid production for anaplerosis [1], transamination does not yield net keto acid production (consuming a keto acid e.g. pyruvate in the process of generating alpha ketoglutarate). Under physiological conditions plasma glutamate concentration, 10-20uM, is limiting for GDH flux supplying TCA intermediates while plasma glutamine concentration, 600uM, is not [2]. The conversion of  $^{15}\text{N}$  amide labeled glutamine to  $^{15}\text{N}$  ammonium (**Figure1, Rxn1**) approximates the net glutaminase flux generating glutamate and ammonium, both potential substrates for GDH. Indeed GDH can also incorporate the amide derived  $^{15}\text{N}$  ammonium and alpha ketoglutarate into glutamate (**Figure 1, Rxn3**, reductive amination) which can subsequently transaminate with pyruvate generating  $^{15}\text{N}$  alanine [3]. Noteworthy this glutaminolytic anabolic pathway providing glutamate has been proposed as the primary metabolic transformation in tumor cells [4]. **Figure 1, Rxn 3** also illustrates how ammonium production from the  $^{15}\text{N}$  amide of glutamine may underestimate the true glutaminase flux; to the extent that this occurs, it contributes to differences in estimated net glutaminase fluxes between the chemically measured glutamine disappearance and  $^{15}\text{N}$  amide ammonium appearance. Glutamine labeled with  $^{15}\text{N}$  in the amino position provides

an assessment of net GDH flux (**Figure 1,Rxn1**) as  $^{15}\text{N}$   $\text{NH}_4^+$  and, or, ALT flux as  $^{15}\text{N}$  alanine produced(**Figure1,Rxn2**).



**Figure 1. GDH determines the fate of  $^{15}\text{N}$  glutamine.** Pathways of glutaminolysis, net keto acid production and  $\text{NH}_4^+$  produced per glutamine consumed ratio. [1] Deamidation coupled to GDH deamination yielding  $2\text{NH}_4^+/\text{Gln}$  and net keto acid ( $\alpha\text{KG}$ ). [2] Deamidation coupled to ALT-mediated transamination yielding  $1\text{NH}_4^+/\text{Gln}$  and no net acid production. [3] Deamidation coupled to GDH reductive amination and transamination yielding  $<1\text{NH}_4^+/\text{Gln}$  and net keto acid

## 2. Glutamine is the major source of ammonium produced in cultured cells

Because the bulk ( $\approx 90\%$ ), [1,3-5] of the ammonium produced by cells in culture derives from glutamine's 2 nitrogen moieties (preformed DMEM media glutamate is  $<50\mu\text{M}$ ) chemical measures of ammonium produced (after subtracting any ammonium produced in the absence of glutamine) and glutamine consumed offers an index of the GDH pathway activity. A ratio of 1, for example, would be consistent with glutamine metabolized by glutaminase with  $\text{NH}_4^+$  released to the media and glutamate either released to the media or transaminated to amino acids e.g. alanine (**Figure 1, Rxn2**). In either case there is no net GDH flux and therefore no net generation of keto acids. In contrast a ratio of 2  $\text{NH}_4^+/\text{glutamine}$  (**Figure 1, Rxn1**) is consistent with glutamine metabolized by glutaminase and the glutamate produced metabolized by GDH yielding  $\text{NH}_4^+$  and net keto acid (anaplerosis) for the TCA cycle (running in either the normal forward or reverse direction, [6]). On the other hand, an  $\text{NH}_4^+$  produced per glutamine consumed less than 1 (**Figure 1, Rxn3**) is consistent with glutaminase generating  $\text{NH}_4^+$  from the amide nitrogen with reductive amination [3,4] catalyzed by GDH reducing the  $\text{NH}_4^+/\text{Gln}$  ratio to less than 1 producing glutamate and consuming net keto acid (alpha ketoglutarate); subsequent transamination yields amino acids (e.g. alanine, aspartate) consuming keto acids (cataplerosis) containing the amide nitrogen of glutamine [3,4]. Normal breast cell line exhibits an  $\text{NH}_4^+/\text{glutamine}$  ratio less than 1 [7] whereas cancerous breast cell lines exhibit a ratio greater than 1 [7] consistent with a quantitative difference in bidirectional GDH fluxes between normal (reductive amination) and tumorigenic cells (oxidative deamination). In

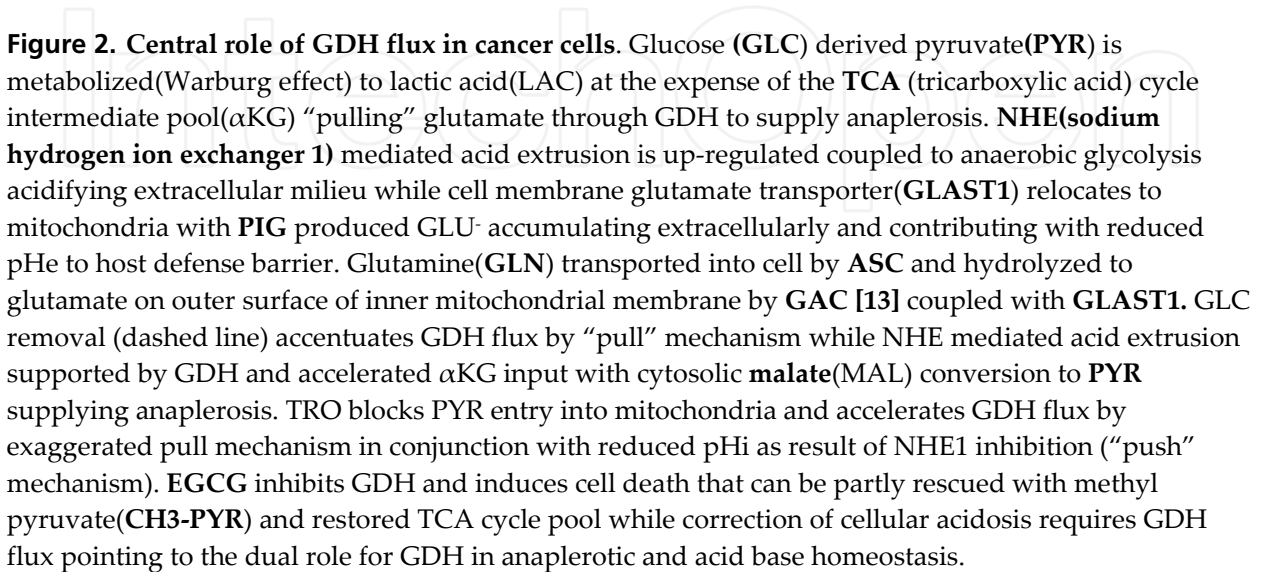
addition, in vivo administered [2-(14)C] labeled glutamate was taken up by tumors with 14C distributed more into protein and lactate than in normal tissues [ 8 ]. In line with this early finding, a recent study[9] showed[U-(13)C] glucose contributed less than 50% of the acetyl COA pool in human brain tumors consistent with glutaminolysis and GDH's role in maintaining TCA pool homeostasis (anaplerosis).

### 3. Intracellular glutamate and alpha ketoglutarate are in near equilibrium

In most cells intracellular glutamate and alpha ketoglutarate are in near equilibrium[4,10], and changes in TCA cycle intermediates( $\alpha$ KG) as well as the redox state(NADPH/NADP), energy charge(ADP,GTP) and cell pH shift the GDH catalyzed flux to net production or consumption of  $\alpha$ KG (**Figure 2**). Normally pyruvate (glucose) provides the TCA cycle with pool intermediates while generated glutamate is transaminated ( $\text{NH}_4^+/\text{GLN}$  ratio<1, **Figure 1 Rxn3**). In cancer cells, glucose is shunted into aerobic glycolysis (Warburg effect, [11]) and the TCA cycle intermediates are reduced as the result of cataplerosis as evidenced by lower intracellular glutamate [7]. This reduction in TCA cycle intermediates “pulls” glutamate through GDH generating  $\alpha$ KG as evidenced by the higher steady state  $\text{NH}_4^+/\text{GLN}$  ratio>1, **Figure 1, Rxn1** and consistent with glutamate (glutaminolysis) supporting anaplerosis (**Figure 2**). As a corollary, the ammonium to alanine produced ratio increases [7] reflecting the increased GDH and decreased ALT flux as the result of reduced intramitochondrial pyruvate(metabolized in cytosol to lactate, **Figure 2**). Thus the increased glutamate flux through GDH generates  $\alpha$ KG while sparing keto acid consumption (reduced transamination).

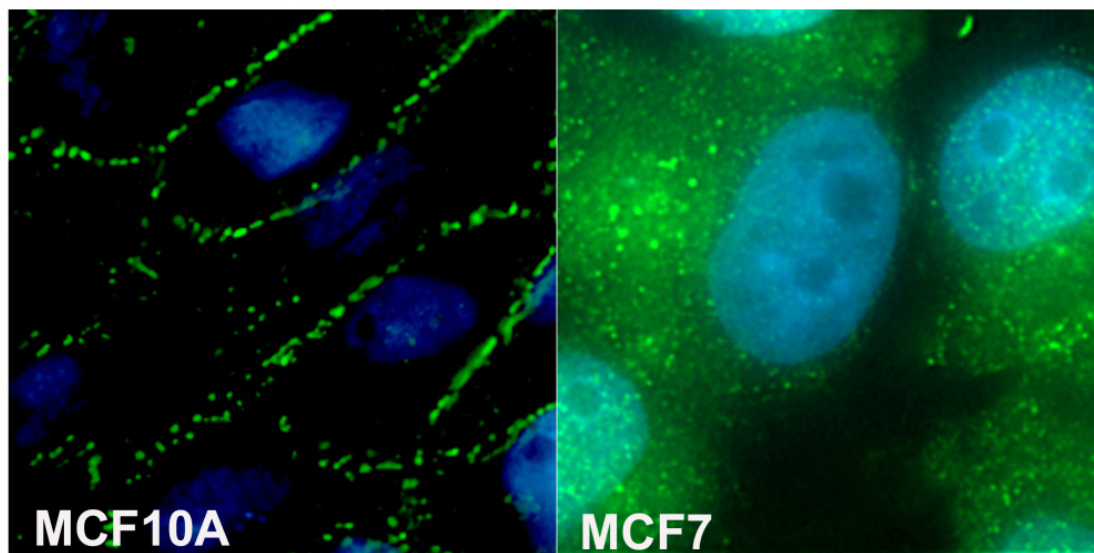
### 4. Glutamate is generated by extra- and intracellular glutaminases

Glutaminolysis as illustrated in **Figure 2** is associated with the increased expression of both the extrinsic cell membrane phosphate independent glutaminase/gamma glutamyltransferase/gamma glutamyltranspeptidase (PIG, GGT, GGTP) which generates extracellular glutamate [2,12] and intracellular phosphate dependent glutaminases, Phosphate dependent glutaminases (PDG, GLS1 and GAC, [13,14]) which generates glutamate cytosolically [2,13]; extracellular glutamate can be transported(GLAST, **Figure2**) into the cytosol functioning as an inhibitor of the intracellular glutaminases[2]. Noteworthy, c-myc signaling up-regulates both the cell membrane glutamine transporter (ASC, **Figure 2**) and the intracellular glutaminases in cancer cells [15]. On the other hand, increased expression of the extracellular PIG is also a hallmark of cancer cells [16] and PIG hydrolysis of  $\gamma$ -glutamyl-tagged fluorescent markers can be used to delineate tumor boundaries [16]. However, in contrast to glutamine uptake, cell membrane glutamate transport (GLAST1) is shifted from the cell membrane to an intracellular location in breast cancer cells as shown in **Figure 3**, effectively uncoupling extracellular glutamate from inhibiting the intracellular glutaminases; this allows full blown expression of intracellular glutamate generation(**Figure 1RXI**) and, if the relocated glutamate transporter, GLAST1 transports glutamate from the outer surface of inner mitochondrial membrane into the into the mitochondria matrix [17],





then it would supply GDH glutamate in support of anaplerosis . Noteworthy overexpression of PIG promotes tumorigenesis [16] presumably by building up extracellular glutamate and suppressing local immune responses [18] . In addition NHE mediated acid extrusion is up-regulated in cancer cells [19,20] importing a  $\text{Na}^+$  load requiring  $\text{Na}^+/\text{K}^+$  ATPase - ATP expenditure and ATP regeneration associated with acidogenic aerobic glycolysis(Warburg effect) and by substrate level phosphorylation. Because PIG (GGT/GGTP), NHE, glutamine transporter and glutaminase activities are all up-regulated in rapidly growing tumors, tagging molecular target inhibitors [21-24] with a  $\gamma$ -glutamyl moiety offers a tumor specific vehicle specific for limiting anaplerosis and preventing elevated cell pH, prerequisites for rapid tumor growth.

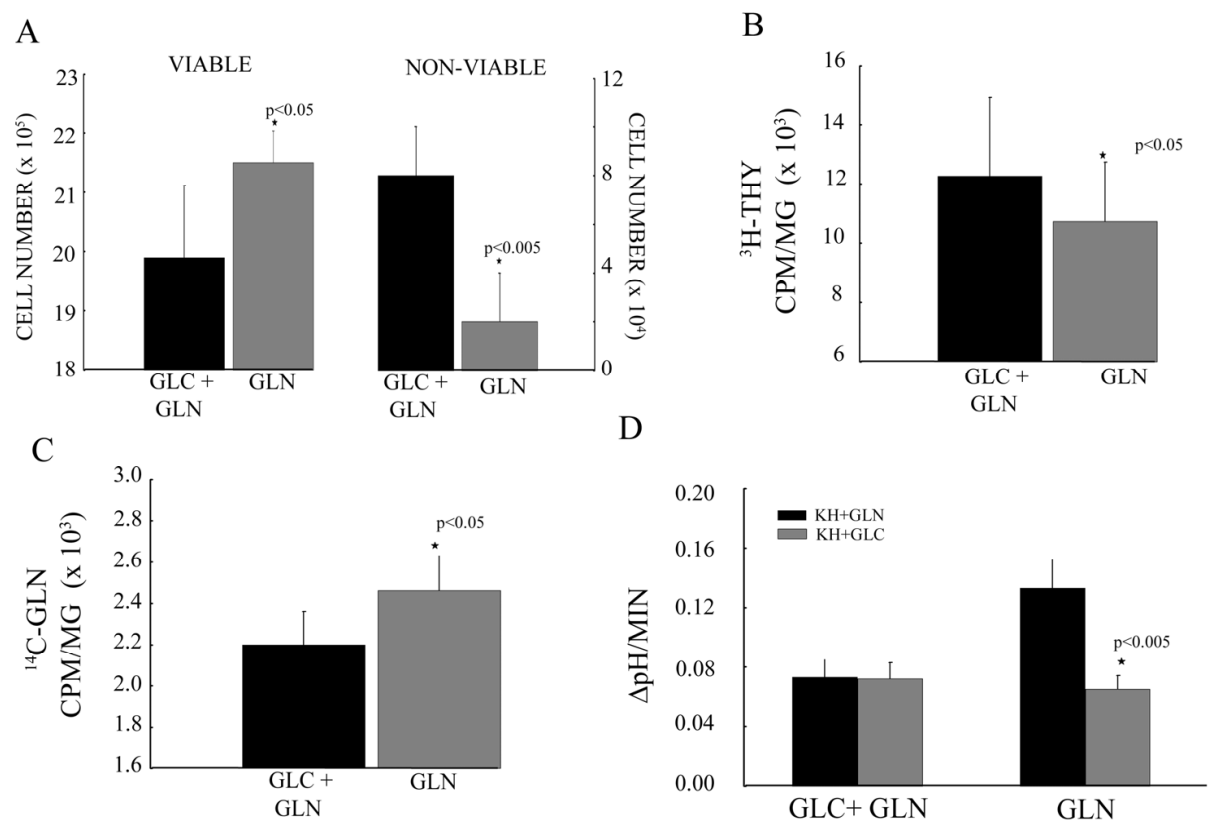


**Figure 3.** GLAST localization in normal versus cancer cells. MCF10A and MCF7 cells cultured on coverglass were stained with monoclonal antibodies to GLAST-1 . MCF10A demonstrate almost complete membrane localization of the transporter, while MCF7 have a cytoplasmic distribution pattern.

## 5. Glucose removal lowers TCA cycle intermediates and “pulls” glutamate through GDH

Removal of glucose from the media (Figure 2, dotted gray line from GLC) deprives cells of pyruvate input into the TCA cycle and a fall in the intermediate ( $\alpha\text{KG}$ ) pool level[5] as reflected by a drop in glutamate [7]. As a consequence, GDH flux (**Figure 1, Rxn1**) increases [5] supplying anaplerosis as malate exits the cycle forming pyruvate which in turn supports citrate formation (**Figure 2**). Noteworthy this increased glutamate flux through GDH(“pulling” effect) is maintained by 2 responses:1] by a small increase in glutaminase flux [5,7] and, 2] a large fall in glutamate transamination [5,7,25]. Under glucose deprivation cell survival is dependent on GDH flux at least in part to supply anaplerosis [5,26]. Surprisingly cell number actually increase in the glutamine (1.3mM) alone compared to the glucose(5mM) plus glutamine media (**Figure 4A**) because of reduced cell death; this increased survival is attributed to the increased GDH flux [26]

which besides supporting anaplerosis also enhances NHE mediated acid extrusion (**Figure 4D**) although proliferation rate decreases (**Figure 4B**). Noteworthy is the increase in cell biomass (protein, nucleic acids and lipid) dependent upon glutaminolysis supported anaplerosis as shown by the increased incorporation of  $^{14}\text{C}$ -U-glutamine into cell biomass (**Figure 4C**). The critical role of GDH flux in cell survival is evident from the massive cell death induced by GDH inhibition under glucose depleted conditions with 100uM EGCG [5,26], an inhibitor of GDH [5]. Although supplying TCA cycle intermediates e.g. methyl pyruvate (10mM, **Figure 2**) rescued cells with GDH inhibited [5,26], a significant fraction of the population succumbed associated with a reduced cell pH [26]. Parenthetically, methylpyruvate is a strong acid constituting a large acid load which requires supplementing the media with equal moles of bicarbonate (10mM). Nevertheless, even after the above base compensation, supplying anaplerotic substrates does not restore NHE activity [26] pointing to an important dual role for GDH in maintaining both anaplerosis and pH homeostasis [22] for cell survival.



**Figure 4.** Physiological (1.3mM) glutamine concentration alone supports breast cancer cell survival associated with increased anaplerotic and acid extrusion function. 4A GLN increased cell number and decreased cell death compared to GLN plus 5mM glucose; 4B Gln slows cell proliferation compared with GLC+GLN; 4C GLN supports anaplerotic function [ $^{14}\text{C}$ -U-L-glutamine incorporation into TCA precipitated cellular protein and lipid 4D GLN supports accelerated NHE activity when assayed with K 10mM GLN as opposed to 10mM GLC

## 6. Cellular acidosis “pushes” glutamate through GDH

Glutamate flux through GDH can be also be “pushed” by a fall in intracellular pH [27]. Whether this reflects a shift from GHD1 to GDH2 isoform [28] is not known but, if so, this “pushing effect” of reduced pH effect could be additive with the above “pulling effect” of a reduced TCA pool (Figure 2). Indeed in metabolic acidosis, the ambient condition surrounding cancer cells in vivo, kidney cells’ glutaminolysis is both “pushed”(reduced cell pHi, [27]) and “pulled”(inhibition of TCA, [29]) as a result of reduced TCA cycle pool size associated with true renal growth [30]. Interestingly enough, the in vivo kidney switches fuels from lactate to glutamine oxidation in metabolic acidosis[31] so that the anaplerotic glutaminolysis-GDH reactions matches [32] the cataplerotic reactions( $\text{CO}_2$ , biomass formation, [30,31] as does acid excretion ( $2\text{NH}_4^+$ /glutamine) and base( $2\text{HCO}_3^-$ /glutamine) generation. Furthermore the pH-dependent enlistment of GDH2 isoform alone (push mechanism) or accompanying GDH 1 flux (anaplerosis driven pull mechanism) would provide regulatory options in responding to anaplerotic/cataplerotic and, or, acid /base demands in tumors.

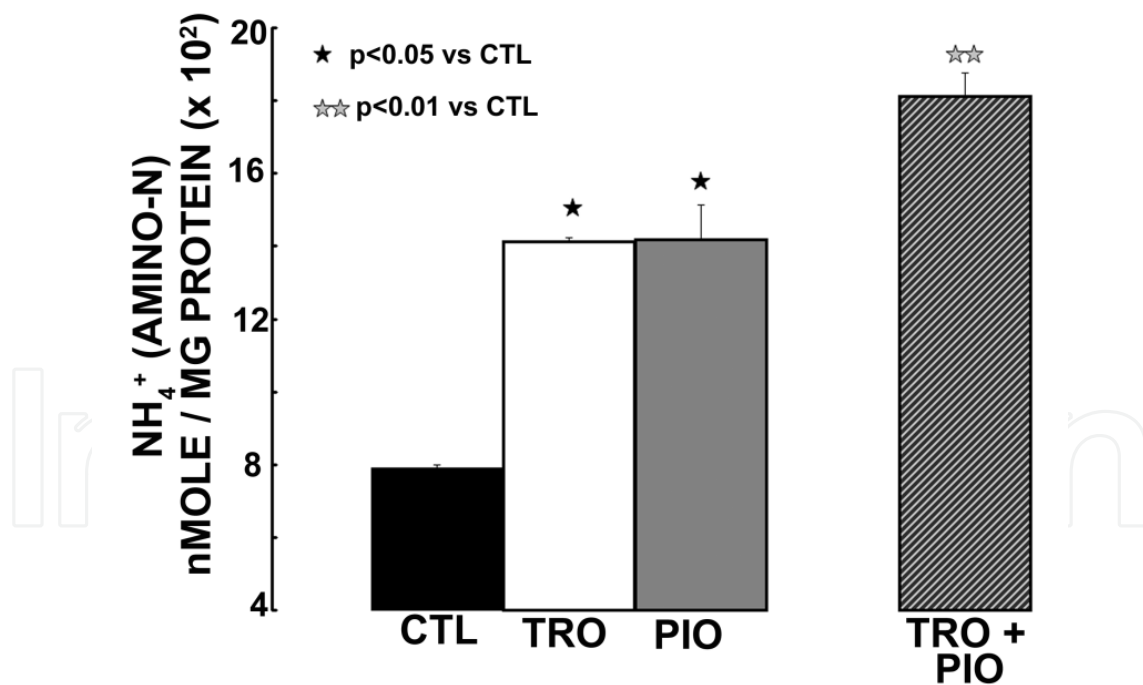
## 7. Glitazones accelerate GDH flux via the push/pull mechanism:

### A strategy for therapeutic intervention

Fortuitously there are agents that can be employed to impose this push/pull mechanism on the GDH flux in cancer cells and thereby present a window of vulnerability (targeted inhibitors). The antihyperglycemic agents, troglitazone (Rezulin) and rosiglitazone (Avandia) block pyruvate entrance into the TCA cycle[25,33] lowering  $\alpha\text{KG}$ (glutamate,7,25] and accelerating GDH flux via this “pull” mechanism (Figure 2). Simultaneously, both troglitazone and rosiglitazone directly inhibit NHE [25,34] lowering pHi and driving GDH via the “push” mechanism (Figure 2). Noteworthy the glutaminase flux (glutamine disappearance) remains unchanged while the  $\text{NH}_4^+$  production increases as the result of the increase in deamination flux (GDH Figure 1, Rxn1). Although resembling glucose deprivation (“pull” mechanism), troglitazone further increases the  $\text{NH}_4^+$  production (additive “push+pull” mechanism) exceeding the fall in alanine production (“pull” mechanism alone). More specifically the accelerated GDH flux (“push+pull”) induced by troglitazone can be demonstrated using  $^{15}\text{N}$  amino labeled glutamine as shown in Figure 5; in contrast, another glitazone pioglitazone(Actos) activates GDH flux [34] solely by reducing cell pH(“push” mechanism) and consequently does not reduce alanine production [34]. Noteworthy troglitazone acutely inhibits GDH flux (0-3hrs) as the result of a fall in mitochondrial membrane potential(  $\Psi\text{m}$ ) requiring accelerated GDH flux(3-24hrs) to fully restore the  $\Psi\text{m}$  [7], a response that is  $\text{PPAR}\gamma$  independent [7,25] and possibly mitoNEET [35] dependent. Little recognized is the direct inhibition of NHE[20,34] by both troglitazone and rosiglitazone as well as indirect inhibition mediated through  $\text{PPAR}\gamma$  suppression of NHE gene expression[20,36]; in contrast, pioglitazone does not inhibit NHE directly[34] rather acts indirectly through  $\text{PPAR}\gamma$ [36]lowering cell pH[34] and accelerating GDH flux(“push” mechanism). In combination, TRO +PIO together exert an additive effect on GDH flux



presumably reflecting both TRO's "pull" action and PIO's PPAR $\gamma$ - mediated down-regulation of NHE gene expression. Significantly, the dual effect of glitazones to increase GDH flux while reducing NHE activity decreases proliferation(NHE) but increases cell survival(GDH) resulting in only a slight decrease in cell number[26]. Nor does adding troglitazone to glucose deleted cells induce massive cell death since the effect on GDH flux is additive (further reducing TCA intermediates and cell pH, **Figure 2**) and although proliferative rates are decreased, survival is enhanced [26]. Under these conditions, e.g. cell survival mechanisms, inhibition of GDH is most effective in causing massive cell death as occurs with the GDH inhibitor EGCG [5] combined with troglitazone [26]. Although rescue of cells is partly possible by restoring anaplerosis with methyl pyruvate, failure to restore NHE activity and the cellular acidosis preclude full recovery underlining the importance of both GDH and NHE in cell survival[26].



**Figure 5. Ammonium production from amino nitrogen of glutamine.** Cells were incubated for 18 hours in [2-15N] glutamine. TRO was used at 20  $\mu\text{M}$ , PIO 10  $\mu\text{M}$ . Results are from 3 experiments.

## Author details

Ellen Friday

*Department of Medicine- Feist- Weiller Cancer Center*

*Department of Cellular and Molecular Physiology, Louisiana State University Health Sciences Center, Shreveport, LA, USA*

Robert Oliver III and Tomas Welbourne

*Department of Cellular and Molecular Physiology, Louisiana State University Health Sciences Center, Shreveport, LA, USA*

Fancesco Turturro

*Department of Lymphoma; Myeloma, MD Anderson Cancer Center, Houston, TX, USA*

## Acknowledgement

The authors would like to acknowledge the support from the Feist-Weiller Cancer Center (EF and FT) and The Southern Arizona Research Foundation (TW).

## 8. References

- [1] DeBerardinis RJ, Mancuso A, Daikhin E, Nissim I, Yudkoff M, Wehrli S, Thompson CB.(2007) Beyond aerobic glycolysis: Transformed cells can engage in glutamine metabolism that exceeds the requirement for protein and nucleotide synthesis. *Proc Natl Acad Sci.* 104:19345-19350.
- [2] Welbourne T, Routh R, Yudkoff M, Nissim I.(2001) The glutamine/glutamate couplet and cellular function. *News Physiol Sci.*16:157-160.
- [3] Welbourne, T., Friday E, Fowler R, Turturro F, Nissim I.(2004) Troglitazone acts by PPARgamma dependent and PPARgamma-independent pathways on LLC-PK1-F+ acid base metabolism. *Am J Physiol Renal Physiol.* 286:F100-110.
- [4] Meng M, Chen S, Lao T, Liang D, Sang N. (2010) Nitrogen anabolism underlies the importance of glutaminolysis in proliferating cells. *Cell Cycle* 9:3921-3932.
- [5] Yang C, Sudderth J, Dang T, Bachoo RM, McDonald JG, DeBerardinis RJ.(2009) Glioblastoma cells require glutamate dehydrogenase to survive impairments of Akt signaling. *Cancer Res* 69:7986-7893.
- [6] Mullen AR, Wheaton WW, Jin ES, Chen PH, Sullivan LB, Cheng T, Yang Y, Linehan WM, Chandel NS, DeBerardinis RJ. (2011) Reductive carboxylation supports growth in tumor cells with defective mitochondria. *Nature* 481:385-38
- [7] Friday E, Oliver R 3rd, Welbourne T, Turturro F. (2011) Glutaminolysis and glycolysis regulation by troglitazone in breast cancer cells: relationship to mitochondrial membrane potential. *J. Cell Physiol* 226:511-519.
- [8] Nyhan WL, Busch H. (1958) Metabolic patterns for glutamate-2-C14 in tissues of tumor bearing rats. *Cancer Res.* 18:385-393.

- [9] Maher EA, Marin-Valencia I, Bachoo RM, Mashimo T, Raisanen J, Hatanpaa KJ, Jindal A, Jeffrey FM, Choi C, Madden C, Mathews D, Pascual JM, Mickey BE, Malloy CR, Deberardinis RJ. (2012) Metabolism of [U-(13)C] glucose in human brain tumors in vivo. *NMR Biomed* 15 doi 10.1002/nbm.2794
- [10] Silverstein E, Sulebele G.(1974) Equilibrium kinetic study of the catalytic mechanism of oxidative deamination of alanine by bovine liver glutamate dehydrogenase. *Biochemistry* 13:1815-1818.
- [11] Warburg, O. (1956) On the origin of cancer cells. *Science*. 123: 309-314
- [12] Wong KT, Lee YY, Brusica V, Tan J, Yap MG, Nissom PM (2005) Elevation of gamma glutamyltransferase activity in 293 HEK cells constitutively expressing antisense glutaminase mRNA. *Metab Eng* 7:375-383.
- [13] Kvamme E, Nissen-Meyer LS, Roberg BA, Torgner IA. (2008) Novel form of phosphate activated glutaminase in cultured astrocytes and human neuroblastoma cells, PAG in brain pathology and localization in the mitochondria. *Neurochem Res* 33:1341-1345.
- [14] Cassago A, Ferreira AP, Ferreira IM, Fornezari C, Gomes ER, Greene KS, Pereira HM, Garratt RC, Dias SM, Ambrosio AL. (2012) Mitochondrial localization and structure-based phosphate activation mechanism of glutaminase C with implications for cancer metabolism. *Proc Natl Acad Sci USA* 109:1092-1097.
- [15] Wise DR, DeBerardinis RJ, Mancuso A, Sayed N, Zhang XY, Pfeiffer HK, Nissim I, Daikhin E, Yudkoff M, McMahon SB, Thompson CB.(2008) Myc regulates a transcriptional program that stimulates mitochondrial glutaminolysis and leads to glutamine addiction. *Proc Natl Acad Sci U S A*. 105: 18782-18787.
- [16] Urano Y, Sakabe M, Kosaka N, Ogawa M, Mitsunaga M, Asanuma D, Kamiya M, Young MR, Nagano T, Choyke PL, Kobayashi H.(2011) Rapid cancer detection by topically spraying a  $\gamma$ -glutamyltranspeptidase-activated fluorescent probe. *Sci Trend Med* 31:110 -119
- [17] Bauer DE, Jackson JG, Genda EN, Montoya MM, Yudkoff M, Robinson MB.(2012) The glutamate transporter ,GLAST, participates in a macromolecular complex that supports glutamate metabolism. *Neurochem Int*. doi 10.1016/j.neuint.2012.01.013
- [18] Dröge W, Eck HP, Betzler M, Schlag P, Drings P, Ebert W.(1988) Plasma glutamate concentration and lymphocyte activity. *J Cancer Res Clin Oncol* 114:124-128.
- [19] Reshkin SJ, Bellizzi A, Caldeira S, Albarani V, Malanchi I, Poignee M, Alunni-Fabbroni M, Casavola V, Tommasino M.(2000) Na<sup>+</sup>/H<sup>+</sup> exchanger-dependent intracellular alkalinization is an early event in malignant transformation and plays an essential role in the development of subsequent transformation-associated phenotypes. *FASEB J* 14:2185-97.
- [20] Turturro F, Friday E, Fowler R, Surie D, Welbourne T.(2004) Troglitazone acts on cellular pH and DNA synthesis through a peroxisome proliferator-activated receptor gamma-independent mechanism in breast cancer-derived cell lines. *Clin Cancer Res*. 10:7022-7030.

- [21] García-Cañero R, Trilla C, Pérez de Diego J, Díaz-Gil JJ, Cobo JM.(1999) Na<sup>+</sup>/H<sup>+</sup> exchange inhibition induces intracellular acidosis and differentially impairs cell growth and viability of human and rat hepatocarcinoma cells. *Toxicol Letts* 106:215-228.
- [22] Schelling, JR, Abu Jawdeh, BG. (2008) Regulation of cell survival by Na<sup>+</sup>/H<sup>+</sup> exchanger-1. *Am J Physiol Renal Physiol*. 295:F265-632.
- [23] Fuchs BC, Finger RE, Onan MC, Bode BP.(2007) ASCT2 silencing regulates mammalian target-of-rapamycin growth and survival signaling in human hepatoma cells. *Am J Physiol Cell Physiol*.. 293:C55-63
- [24] Hartwich,EW., Curthoys,NP. (2011) BPTES inhibition of hGA(124-551), a truncated form of human kidney  $\gamma$ -type glutaminase. *J Enzyme Inhib Med Chem* doi:10.3109/14756366.2011.622272)
- [25] Oliver R 3rd, Friday E, Turturro F, Welbourne T.(2010) Troglitazone regulates anaplerosis via a pull/push affect on glutamate dehydrogenase mediated glutamate deamination in kidney derived epithelial cells; implications for the Warburg effect. *Cell Physiol Biochem* 26:619-628.
- [26] Friday E, Oliver R, III, Turturro F, Welbourne T. (2011) Enhancing glutaminolysis in glutamine dependent breast cancer cells with TRO provides a therapeutic window for GDH inhibition by EGCG inducing massive cell death. *FASEB J*. 25: 915.8.
- [27] Nissim I, Sahai A, Sandler RS, Tannen RL (1994) The intensity of acidosis differentially alters the pathways of ammoniagenesis in LLC-PK1 cells. *Kidney Int*. 45:1014-1019.
- [28] Spanaki,C., Plaitakis,A.(2012) The role of glutamate dehydrogenase in mammalian ammonia metabolism . *Neurotox Res* 21:117-127.
- [29] Nissim, I, Nissim I, Yudkoff M. (1990) Carbon flux through TCA cycle in rat renal tubules.*Biochim Biophys Acta* 1033:194-200.
- [30] Lotspeich, W. (1967) Metabolic aspects of acid base change. *Science* 155:1066-1075.
- [31] Pitts,RF. (1975) Production of CO<sub>2</sub> by the intact functioning kidney of the dog *Med Clin N Am* 59:507-517.
- [32] Owen OE, Kalhan SC, Hanson RW. (2002) The key role of anaplerosis and cataplerosis for citric acid cycle function. *J Biol Chem*.. 277:30409-30412
- [33] Fediuc S, Pimenta AS, Gaidhu MP, Ceddia RB (2008) Activation of AMP-activated protein kinase, inhibition of pyruvate dehydrogenase activity, and redistribution of substrate partitioning mediate the acute insulin-sensitizing effects of troglitazone in skeletal muscle cells. *J Cell Physiol*. 215:392-400.
- [34] Turturro F, Oliver R 3rd, Friday E, Nissim I, Welbourne T. (2007) Troglitazone and pioglitazone interactions via PPAR $\gamma$  independent and  $\gamma$ -dependent pathways in regulating physiological responses in renal tubule-derived cell lines. *Am J Physiol Cell Physiol* 292:C1137-1146.
- [35] Feinstein DL, Spagnolo A, Akar C, Weinberg G, Murphy P, Gavriluyuk V, Dello Russo C.(2005) Receptor-independent actions of PPAR thiazolidinedione agonists: is mitochondrial function the key. *Biochem Pharm*. 70:177-188.

- [36] Kumar AP, Quake AL, Chang MK, Zhou T, Lim KS, Singh R, Hewitt RE, Salto-Tellez M, Pervaiz S, Clément MV (2009) Repression of NHE1 expression by PPARgamma activation is a potential new approach for specific inhibition of the growth of tumor cells in vitro and in vivo. *Cancer Res.* 69:8636-8644.

IntechOpen

IntechOpen