

# Rewiring of glycolysis in cancer cell metabolism

Jason W. Locasale<sup>1,2,\*</sup> Matthew G. Vander Heiden<sup>3,4</sup> and Lewis C. Cantley<sup>1,2,\*</sup>

<sup>1</sup>Department of Systems Biology; Harvard Medical School; <sup>2</sup>Division of Signal Transduction; Beth Israel Deaconess Medical Center; Center for Life Science; Department of Medicine; <sup>3</sup>Department of Medical Oncology; Dana Farber Cancer Institute; Harvard Medical School; Boston, MA USA; <sup>4</sup>Koch Institute for Integrative Cancer Research; Department of Biology; Massachusetts Institute of Technology; Boston, MA USA

Altered metabolism constitutes a nearly universal feature of cancer cells.<sup>1</sup> This metabolic reorganization in part originates from the high proliferative state displayed by cancer cells. The nature of this altered metabolism is complex with multiple strategies implemented across diverse contextual dependencies to enable the accumulation of the biomass that is necessary for proliferation in a stressful tumor microenvironment.<sup>2</sup>

Proliferating cancer cells have differential requirements for the synthesis of nucleic acid, protein and lipid constituents.<sup>3</sup> Regulation of cellular redox status is another essential metabolic need that must be accommodated in transformed cells. This may lead to an alteration of glucose metabolism that allows for the diversion of glycolytic flux into biosynthetic pathways such as the pentose phosphate pathway. Such a rewiring may also indirectly interact with mitochondrial tricarboxylic acid cycle (TCA) flux to allow for enhanced biosynthesis and generation of reducing equivalents from TCA cycle intermediates. However, in order to direct the movement of the appropriate carbon skeletons into the necessary anabolic and oxidative stress-protective pathways, changes in cofactor availability that define cellular redox state and energy status for metabolic enzymes are required. These cofactors include those that couple electron transfer during cellular redox reactions (such as NADH and NADPH) as well as nucleotides that regulate energy status and other functions such as ATP and GTP.<sup>4</sup>

It is often assumed that cancer cell metabolism may be adapted to meet high

energy requirements in proliferating cells. However, basal cellular processes likely consume more ATP than the combined processes required for cell proliferation.<sup>5</sup> For example, active transport through ion channels is believed to constitute at least 50% of the ATP consumption in cells. Furthermore, the stoichiometric requirements for glycolysis mandate that sufficient ATP be consumed in order to maintain high fluxes through central carbon metabolism. Historically, efforts to explain this high glycolytic flux concentrated on mechanisms involving the upregulation of ATP consumption.<sup>6</sup> For example, there was considerable effort to identify changes in ion channel fluxes that may accompany differences in glycolytic metabolism.

One clue to how cancer cells might achieve some of these metabolic demands has recently come into focus. This was the observation that almost all cancer cells appear to adopt expression of a single isoform of pyruvate kinase (PKM2) that is normally expressed during embryonic development and in other proliferating tissue.<sup>7</sup> PKM2 is intrinsically a less active enzyme and is also subject to negative regulation by phosphotyrosine signaling that is often upregulated in cancer cells.<sup>8</sup> Why a less active enzyme is present in cells with enhanced glycolysis has been a mystery.

A recent study from our laboratory provides a potential explanation of this selectivity towards PKM2.<sup>9</sup> Evidence is presented for a previously uncharacterized glycolytic pathway that metabolizes glucose to pyruvate even in the absence of pyruvate kinase activity. This paper shows that the substrate for pyruvate

kinase, phosphoenolpyruvate (PEP), can donate its phosphate to the enzyme phosphoglycerate mutase (PGAM). PGAM accepts the phosphate from PEP that in turn primes the enzyme for additional catalytic activity. This creates a positive feedback loop whereby PEP can increase the upstream activity of the glycolytic pathway. Additionally, this reaction was associated with pyruvate generation, presumably through a tautomerization reaction following the loss of the phosphate group on PEP. Furthermore, this alternate pathway was enhanced in PKM2 expressing cells.

Despite this intriguing finding, questions remain. The enzyme responsible for this PEP-dependent histidine kinase activity has not been identified. Also, the precise mechanism by which this alternate pathway is coupled to the loss of inorganic phosphate from the cycle as an alternative to its donation to ADP remains unknown. Nevertheless it is exciting that more than 80 years after the initial discovery of aerobic glycolysis in cancer cells, much remains to be learned about glycolysis and its regulation.

## References

1. Warburg O. *Science* 1956; 123:309-14.
2. Luo J, et al. *Cell* 2009; 136:823-37.
3. Vander Heiden MG, et al. *Science* 2009; 324:1029-33.
4. Locasale JW, et al. *BMC Biol* 2010; 8:3.
5. Kilburn DG, et al. *Cell Sci* 1969; 4:645-7.
6. Racker E. *J Cell Physiol* 1976; 89:697-700.
7. Christofk HR, et al. *Nature* 2008; 452:230-3.
8. Christofk HR, et al. *Nature* 2008; 452:181-6.
9. Vander Heiden MG, et al. *Science* 2010; 329:1492-9.

\*Correspondence to: Jason W. Locasale and Lewis C. Cantley; Email: lewis\_cantley@hms.harvard.edu and JLocasale@bidmc.harvard.edu

Submitted: 10/06/10; Accepted: 10/07/10

Previously published online: [www.landesbioscience.com/journals/cc/article/13925](http://www.landesbioscience.com/journals/cc/article/13925)

DOI: 10.4161/cc.9.21.13925

Comment on: Vander Heiden MG, et al. *Science* 2010; 329:1492-9.