PGAMgnam Style: A Glycolytic Switch Controls Biosynthesis

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Therapeutic strategies that target glycolysis and biosynthetic pathways in cancer cells are currently the main focus of research in the field of cancer metabolism. In this issue of *Cancer Cell*, Hitosugi and colleagues show that targeting PGAM1 could be a way of "killing two birds with one stone".

The metabolism of cancer cells differs from that of many normal cells and is mostly characterized by higher rates of glucose metabolism under normal oxygen levels. This trait enables cancer cells to satisfy their demand for both energy and biosynthetic building blocks required for proliferation. For that reason, it is not surprising that many glycolytic enzymes are commonly overexpressed in tumors (Tennant et al., 2009). Phosphoglycerate mutase (PGAM1) catalyzes the conversion of 3-phosphoglycerate (3PG) into 2-phosphoglycerate (2PG) as part of the glycolytic pathway using a phospho-histidine residue at the enzyme's catalytic domain (His11) as a phosphate donor/acceptor and 2,3-bisphosphoglycerate as an intermediate metabolite (Fothergill-Gilmore and Watson, 1989). In humans, PGAM1 is widely expressed at levels that vary among different tissues as well as during differentiation and transformation. PGAM1 is overexpressed in several types of cancer (Fothergill-Gilmore and Watson, 1989; Ren et al., 2010). Because PGAM1 expression is negatively regulated by the tumor suppressor TP53, the loss of the latter may cause increased expression of PGAM1 in cancer. This portrays PGAM1 as a potential therapeutic target, and indeed, pharmacological inhibition of PGAM1 reduced proliferation of breast cancer cells (Evans et al., 2005). Furthermore, in cancer cells that overexpress the tightly-regulated isoform of pyruvate kinase PKM2, PGAM1 phosphorylation on His11, and hence PGAM1's activity, are induced by phosphoenolpyruvate, the substrate of pyruvate kinase (Vander Heiden et al., 2010).

The notion that metabolites can act as signaling molecules in distant metabolic pathways is gaining significant attention and support (Figure 1A). Some of the best known examples are the activation of PKM2, which catalyzes the last step of glycolysis, by fructose 1,6-bisphosphate (an upstream glycolytic intermediate) and the inhibition of phosphofructokinase-1 (another key regulated glycolytic enzyme) by phosphoenolpyruvate, citrate, and ATP (Ashizawa et al., 1991; Evans et al., 1981). These regulatory loops ensure that glycolytic intermediates are optimally utilized and channeled into the appropriate metabolic pathway to balance energetic and anabolic demands. Recently, the amino acid serine was demonstrated to bind and directly activate PKM2 in order to control the bifurcation point from glycolysis to serine biosynthesis (Chaneton et al., 2012). In line with this concept, this issue of *Cancer Cell* features the work by Hitosugi et al. (2012), which demonstrates that, in addition to their involvement in glycolysis, both the substrate and product of PGAM1 (3PG and 2PG, respectively) modulate two other biosynthetic pathways derived from glycolysis: the oxidative branch of the pentose phosphate pathway (PPP) and the serine biosynthesis pathway (Figure 1A).

Hitosugi et al. (2012) studied the prospective therapeutic approach of PGAM1 inhibition in cancer cells and the associated metabolic consequences. Silencing the expression of PGAM1 with short-hairpin RNA caused an increase in the intracellular levels of 3PG and a decrease in 2PG levels, which is associated with a block in the glycolytic flow. Surprisingly, the downregulation of PGAM1 levels also inhibited the entry of glucose 6-phosphate into the oxidative PPP, a process which supports de novo nucleotide biosynthesis. Hitosugi et al. (2012) demonstrated that the increase in 3PG directly causes the inactivation of the PPP enzyme 6-phosphogluconate dehydrogenase (6PGD) by competing with its substrate 6-phosphogluconate. What's more, the decrease in 2PG levels upon PGAM1 downregulation was accompanied by a reduction in phosphoglycerate dehydrogenase (PHGDH) activity, which utilizes 3PG as a substrate and carries out the first regulated step in the serine biosynthesis pathway (Figure 1B). Interestingly, the cell permeable analog of 2PG (methyl-2-PG) rescued PGAM1-silenced cells by increasing the flux of 3PG into the serine biosynthesis pathway through PHGDH and, with that, alleviated the inhibition of the PPP by 3PG while also rescuing glycolysis. Furthermore, a screen for small molecule inhibitors of PGAM1 identified an allosteric inhibitor that affected cell metabolism and growth of xenografted tumors in vivo in a manner similar to PGAM1 silencing. These observations strengthen the concept that targeting PGAM1 pharmacologically may be beneficial for cancer therapy not only by reducing an important energy source of cancer cells, but also by preventing anabolic processes required for cell growth and proliferation.

The work by Hitosugi et al. (2012) not only provides new insights into the complex mechanism of metabolic regulation (by identifying 2PG and 3PG as signaling molecules that regulate biosynthetic pathways), but also emphasizes the potential effectiveness of exploiting such complexity, which allows for the targeting of both energetic and anabolic processes with a single drug. However, one of the main challenges in targeting cancer metabolism is the robustness

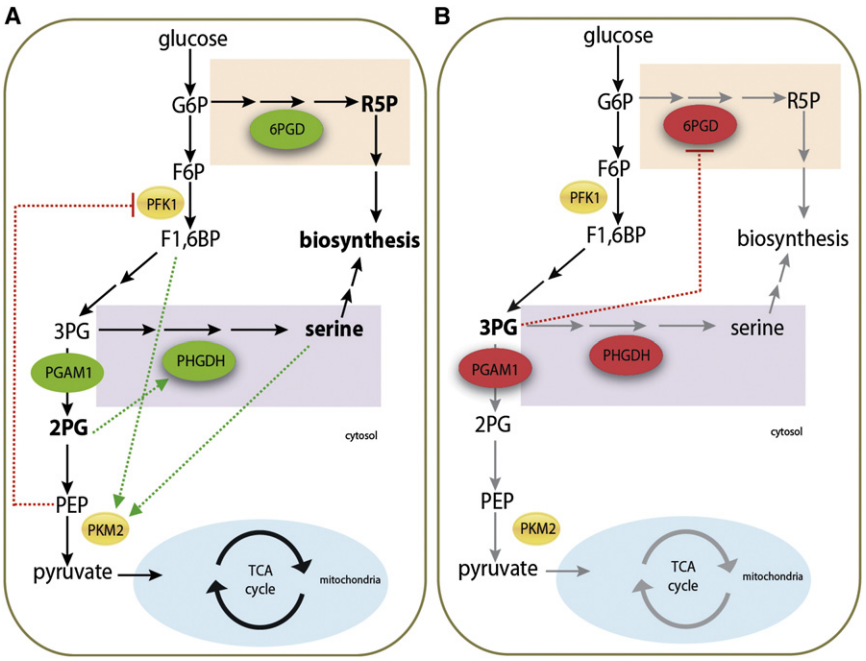

Figure 1. The Dual Catabolic and Anabolic Roles of PGAM1 that Make It a Useful Target for Cancer Treatment

(A) Glycolysis and biosynthetic processes that "branch" from glucose metabolism are required to support growth and proliferation of cells. These processes must be tightly controlled and adjusted to meet cellular needs. Intricate regulatory loop signals exist to enable such control. These include phosphofructokinase-1 (PFK1) inhibition by phosphoenolpyruvate (PEP) and the activation of pyruvate kinase (PK) M2 isoform (PKM2) (the predominant isoform expressed in proliferating cells) by fructose 1,6-bisphosphate (F1,6BP) and serine. PGAM1 is overexpressed in many cancer cells supporting energetic demands by enabling increased glycolytic flux. At the same time, its product 2-phosphoglycerate (2PG) stimulates phosphoglycerate dehydrogenase (PHGDH), which catalyzes the first and rate-limiting step in the serine biosynthesis pathway (purple rectangle).

(B) Upon inhibition of PGAM1, an increase in 3-phosphoglycerate (3PG) and a decrease in 2PG occur. This leads to a decrease in glycolytic flow and energy production by PK as well as the tricarboxylic acid (TCA) cycle in the mitochondria. In addition, the reduction in 2PG due to PGAM1 inhibition prevents the channeling of 3PG into the serine biosynthetic pathway, leading to further accumulation of 3PG. Accumulated 3PG, in turn, inhibits 6-phosphogluconate dehydrogenase (6PGD) in the pentose phosphate pathway (brown rectangle) and ribosome 5-phosphate (R5P) production. In effect, the inhibition of PGAM1, a glycolytic enzyme, not only limits glycolysis, but also two important anabolic processes required for cell proliferation.

Green or red dotted lines indicate direct positive or negative regulatory effects and green or red ovals represent active or inactive enzymes, respectively. Black or gray arrows represent active or inhibited reactions, respectively.

and plasticity of metabolic networks that allow cancer cells to adapt and overcome impediments. In addition, a consideration for long- and short-term toxicity to metabolically active normal tissues must be taken into account when a core glucose metabolic pathway is being targeted. Encouragingly, the in vivo work reported by Hitosugi et al. (2012) demonstrated a good therapeutic index for such a strategy.

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