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RESEARCH HIGHLIGHT

An idle PHGDH takes control of cell fate

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Multifunctional metabolites are widely involved in physiological and pathological processes as signaling molecules, sensors, epigenetic modification substrates and so on, in addition to being energy substances. In a recent *Cell Research* study, Wu et al. make a remarkable discovery that, when the level of 3-phosphoglycerate, a typical metabolite at the crossroads of glucose catabolism and serine anabolism, is low, the unoccupied 3-phosphoglycerate dehydrogenase is redirected to watch the cell fate.

One of the simplest but most precious gifts nature has given to human beings is glucose. It provides energy for biological processes and is involved in biosynthesis in almost all heterotrophic organisms, including humans. Because of its unique structure and involvement in heavily divergent metabolic pathways, glucose can control all aspects of life. The traditional roles of metabolic enzymes and their respective metabolites in glucose metabolism are to provide ATP and biomacromolecules in the course of cellular life. Beyond these roles, metabolic processes have been redefined in recent years by increasing evidence of non-classical functions of metabolic enzymes as well as newly recognized functions of metabolites. Metabolic enzymes are discovered as protein kinases, phosphatases, transcriptional factors, RNA-binding proteins, or secretory proteins; meanwhile, metabolites are found as signal molecules, receptors, sensors, and co-factors or substrates involved in epigenetic modification.[1] In 2017, Lin group reported that the sugar diphosphate fructose-1,6-bisphosphate (FBP) produced during glucose metabolism coupled with its corresponding downstream glycolytic enzyme aldolases (ALDOs) could sense and signal glucose availability, triggering AMPK activation in an AMP/ADP-independent manner.[2] This finding expands our understanding of the fundamental functions of metabolic enzymes and metabolites. Yet, that is not the end of the story.

In a recent study, the Lin group showed that under glucose deprivation conditions, phosphoglycerate dehydrogenase (PHGDH) can sense the loss of glycolytic intermediate 3-phosphoglycerate (3-PGA), and then form a giant complex with the scaffold protein AXIN to phosphorylate p53, thereby triggering apoptosis.[3] It is well known that, in the process of glucose catabolism, there are three branching roads: the well-known G6PD-mediated pentose phosphate pathway (PPP), the GFAT-mediated hexosamine biosynthesis pathway (HBP), and the PHGDH-mediated de novo serine synthesis pathway (SSP) (Fig. 1). Ultraviolet[4] or physiologically low glucose stimulation can trigger cell apoptosis by increasing p53 phosphorylation, but mechanisms underlying cell perception of glucose deprivation and downstream induction of apoptosis remained unknown. To explore whether and which glycolytic metabolites are responsible for this process, the authors knocked down a series of glycolytic enzymes or cultured cells with small-molecule inhibitors targeting glucose metabolism. Through rigorous and ingenious experiments, they identified that 3-PGA reduced during a short period of glucose deprivation is the key intermediate metabolite for low glucose-induced $p53^{S46}$ phosphorylation, rather than other glucose metabolic intermediates, PPP/HBP metabolites or components of AMPK-related signaling pathways.

To identify the molecule that senses 3-PGA levels and is responsible for $p53^{S46}$ phosphorylation, the authors performed immunoprecipitation-mass spectrometry and showed that PHGDH is the staunch binding partner of p53 protein when cells were deprived of glucose. PHGDH mutants that constitutively bind 3-PGA block $p53^{S46}$ phosphorylation induced by low glucose, but the mutants that are unable to bind 3-PGA had the opposing effect. They found that PHGDH, the direct sensor of 3-PGA, transmits the low glucose or low 3-PGA signal to $p53^{S46}$ phosphorylation to induce cell apoptosis and tumor suppression independently of its catalytic activity, by forming a complex protein machinery with AXIN–HIPK2–TIP60–p53 (Fig. 1).[3] Collectively, this fascinating and elegant study showed that the reduction of 3-PGA levels induced by physiological conditions such as calorie restriction controls early cell fate by endowing the gatekeeper PHGDH a new function to transmit $p53^{S46}$ phosphorylation-induced instantaneous apoptosis signals, providing a new paradigm for metabolite regulation of cell fate and enriching the versatility of metabolites in health and disease.

PHGDH expression is enhanced in 70% of triple-negative breast cancers[5] and some other cancers (such as melanoma).[6] Its catalytic activity is important for cancer proliferation by providing serine, glycine, glutathione and one-carbon units (Fig. 1).[5,6] In terms of effects of PHGDH on tumor cell growth, its function does not seem to be simply equivalent to serine production, as it has been shown that the impaired cell growth caused by PHGDH loss cannot be rescued by supplementing exogenous serine.[5] These phenomena suggest that PHGDH has wider and unknown physiological roles.

Recent studies showed that PHGDH promotes tumor growth by regulating transcriptional events in the nucleus[7] or as a translational factor in the mitochondrion[8] independently of serine synthesis (Fig. 1). Although the catalytic activity of PHGDH supports cancer cell proliferation, low PHGDH protein expression (independent of catalytic activity) enhances breast cancer metastasis under heterogeneous conditions.[9] These results suggest that tumor cells play the "two faces" trick, reducing

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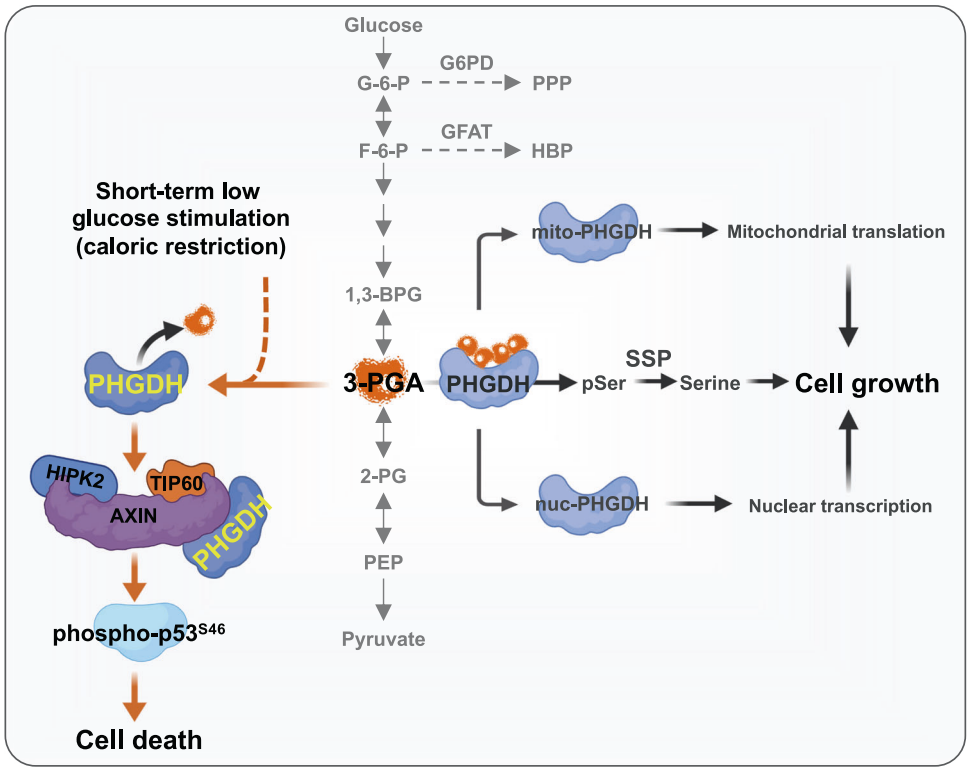

Fig. 1 Low 3-PGA redirects PHGDH to the road not taken. As the first rate-limiting enzyme of the SSP, PHGDH promotes cell proliferation on one hand through amplification and its catalytic activity, and on the other hand, through translocation to the nucleus and mitochondrion to regulate nuclear transcriptional events and mitochondrial translation, respectively (right panel). Herein, Wu et al. showed that under short-term low glucose stimulation (simulating physiological caloric restriction) conditions, PHGDH senses the reduction of 3-PGA, and then the accumulated 3-PGA-unoccupied PHGDH coupled with AXIN–HIPK2–TIP60–p53 to form a supramolecular complex to induce $p53^{S46}$ phosphorylation, leading to early cell death (left panel).

PHGDH expression when they need to metastasize; once they settle down, the expression of PHGDH is upregulated in time to achieve the purpose of rapid proliferation by reactivating its metabolic capacity.[9] More interestingly, phosphoserine (pSer) generated from SSP is enriched by glycolytic enzyme enolases (ENOs). By binding to ENO2, pSer promotes an open active site conformation but has little effect on enolase activity.[10] Inspired by the findings from Lin group, we wonder whether ENOs also sense pSer levels. In short, the extensive interactions of metabolic enzymes (ALDOs, PHGDH, ENOs) and metabolites (FBP, 3-PGA, pSer) between glucose metabolism and serine metabolism indicate that there are a large number of ingenious internal connections in natural metabolic processes that are open to grasp. Metabolites and their corresponding enzymes could be angels or devils, depending on physiological and pathological conditions. More surprises are expected to be unveiled in the future.

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