Reply to Leithner et al.: Focus on phopshoenolpyruvate carboxykinase (PEPCK): A target of the p53-SIRT6-FoxO1 axis

Cancer metabolism has drawn widespread attention since the unique metabolic properties of cancer cells were characterized. We found that p53, a potent tumor suppressor, down-regulates the expression of phopshoenolpyruvate carboxykinase (PEPCK, PCK1) in coordination with histone deacetylase sirtuin 6 (SIRT6) to inhibit tumor cell gluconeogenesis (1). Because p53 is malfunctioning in numerous types of cancer, the p53-SIRT6-forkhead box protein O1 (FoxO1) axis may shed light on the "Warburg effect," a phenomenon in cancer metabolism that has harassed scientists for decades. PCK1 is mainly expressed in liver and kidney, with an increasing expression and maturation after birth. PCK1 is localized in the cytosol and functions as the rate-limiting enzyme responsible for gluconeogenesis. Gluconeogenesis has been mostly ascribed to PCK1 conventionally (2). Considering the unique expression of PCK1 in liver, which is the most important organ in gluconeogenesis and blood glucose maintenance, we may conclude that the p53-SIRT6-FoxO1 axis on PCK1 is critical in gluconeogenic regulation in both normal and tumor cells. However, a recent letter and study by Leithner et al. suggest that the mitochondrial isoform of PEPCK (PEPCK-M, PCK2) may be another key regulator of metabolism and survival in cancer cells (3, 4). PCK2, instead of PCK1, responds to glucose limitation in tumor cells and involves tumor cell death (4). Although less attention has been paid to PCK2 because it has proved to be less enzymatically active than PCK1, nevertheless, based on previous studies of PCK2, we may make a bold speculation that PCK2 might be responsible for basal level gluconeogenesis and PCK1 for hormone and nutrient stimulation, with more flexible regulation. Given the facts that cancer cells have faster metabolism rates and PCK1 is absent or expressed in low levels in many other organs, the seemingly more fundamental PCK2 may be motivated in tumor cells under glucose starvation. In addition, the general expression of PCK2 in most organs other than liver, such as islets, and its mitochondrial location, may endow it with other functions in metabolism besides gluconeogenesis. For example, PCK2 is found to be associated with glucose-stimulated insulin secretion (5). It is possible that PCK2 may play important roles in other metabolic processes in tumor cells with a different mechanism from normal cells to influence cell growth and death. To test these two hypotheses, it is necessary to examine the effect of the p53-SIRT6-FoxO1 axis on PCK2 under both quiescent and stress conditions in normal or tumor cells. It is also critical to compare PCK1 and PCK2 in other models concerning cancer metabolism. Whether PCK1 or PCK2 is more important in regulating gluconeogenesis may be context dependent, based on the cellular background and nutrient supplies. Either way, this topic deserves in-depth discussion and further study. The discrepancy between normal and tumor cells in PEPCK may provide a window to understand cancer metabolism and the Warburg effect.

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