Molecular Biology Reports (2020) 47:8271–8272
https://doi.org/10.1007/s11033-020-05805-9

SHORT COMMUNICATION

PFKP phenotype in lung cancer: prognostic potential and beyond

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Received: 7 June 2020 / Accepted: 3 September 2020 / Published online: 11 September 2020

Abstract

Rapid utilization of glucose is a functional marker of cancer cells, and has been exploited in the clinical diagnosis of malignancies using imaging technology. Biochemically, an increase in the rate of glycolysis, (i.e.) the process of conversion of glucose into pyruvate accelerates the net rate of glucose consumption. One of the critical determinants of glycolytic flux is the enzyme, phosphofructokinase (PFK) which converts fructose-6-phosphate into fructose 1,6, bisphosphate. PFK activity is allosterically inhibited or upregulated by cellular ATP or AMP, respectively. In a recent report of *Cellular Oncology*, Shen et al., have investigated one of the forms of PFK known as the platelet-type PFK (PFKP) in lung cancer. Using clinical samples as well as experimental models the authors unravel the cancer-related roles of PFKP and demonstrate that PFKP phenotype may predict the prognosis of lung cancer. In this letter, the findings are discussed in the light of recent research to expand the potential application and clinical impact of PFKP phenotype in lung cancer.

Keywords Lung cancer · Phosphofructokinase (PFK) · PFK-platelet type (PFKP) · Aerobic glycolysis · Glucose metabolism · Warburg effect

The recent article by Shen et al. [1] on the enzyme, phosphofructokinase platelet-type (PFKP) in lung cancer is very relevant and timely as the role of tumor glycolysis is increasingly evident in tumorigenesis. As a rate-limiting glycolytic enzyme, PFKP regulates glucose metabolism which in turn determines the metabolic phenotype. Using clinical samples as well as in vitro experimental models the authors demonstrate that (i) PFKP expression in lung cancer is associated with overall survival and (ii) down-regulation of PFKP diminishes the rate of glucose uptake resulting in anticancer effects. The study concludes that PFKP may be an indicator of prognosis in lung cancer and its regulatory role in glycolysis may provide a window of opportunity to develop novel therapeutic strategies.

Shen et al., provide compelling data on the significance of PFKP in lung cancer, more importantly, the findings demonstrate that inhibition of PFKP is sufficient to disrupt tumor metabolism, particularly the Warburg effect. Substantial data have established that tumor glycolysis (i.e.) Warburg effect provides selective advantages to cancer cell growth, hence remains a potential therapeutic target [2]. Despite the desirable outcome of antiglycolytic, anticancer strategy in preclinical models, successful clinical translation of such a therapeutic approach remains elusive. From the translational perspective, selection of a candidate tumor that may be sensitive to antiglycolytic treatment continues to be a major impediment. Hence, recently there has been a growing interest to develop predictive strategies to determine the glycolytic and/or metabolic phenotype of cancer to assess its therapeutic vulnerability [3]. Such predictive model approaches may enable us to identify tumors that may qualify for antimetabolic and/or antiglycolytic therapy. As reported by Shen et al., the PFKP may serve as a prognostic marker, nevertheless, exploitation of PFKP to predict metabolic susceptibility may expand its potential to determine (personalized) therapeutic approach.

In lung cancer, glycolytic vulnerability is increasingly evident [4], accordingly elucidation of the metabolic phenotype could distinguish cancers that may respond to antiglycolytic intervention. In this context, the findings of the current report by Shen et al., provides a novel opportunity to assess the predictive potential of PFKP for metabolic targeting. As a critical regulator, PFKP drives glycolysis which in

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turn may elevate lactate production. The acidic metabolite, lactate is transported to external milieu to avoid deleterious effects of intracellular acidification. As the lactate export relies on specific transporters such as monocarboxylate transporters (MCTs), determination of the expression levels of MCTs along with PFKP may provide insights on the anti-glycolytic sensitivity of the particular lung cancer. Noteworthy, PFKP overexpression is not obligatory for MCTs upregulation. For example, as shown by Shen et al., the PFKP levels are increased in both A549 and H520 lung cancer cells lines, whereas the MCTs expression vary between these two cell lines (unpublished data) implying other regulatory mechanisms may control the MCTs and PFKP expression in lung cancers. Thus, confirmation of the expression/activity of both PFKP and MCTs may provide the necessary discernment to select effective therapeutic.

Recently, the tissue microenvironment or the extracellular matrix-related alterations in tissue architecture/stiffness along with cytoskeletal structures have been indicated to affect the rate of glycolysis implying a mechanical-basis for the regulation of glycolytic flux [5]. In lung cancer, among the glycolytic genes, PFKP is the second most upregulated target [5], and has been implicated in overcoming the mechanical-downregulation of glycolysis. Next, besides the PFKP, in lung adenocarcinoma the muscle-type PFK (PFKM) is also upregulated that accelerates glucose metabolism and lactate production [6]. Thus, it is intriguing to understand if the combination of PFKP and PFKM may provide better predictive value in terms of prognosis as well as therapeutic sensitivity to glycolytic/metabolic targeting. The milestone study by Shen et al., generates sufficient interest to further investigate the potential of PFKP phenotype in the prediction of metabolic vulnerability of lung cancer to select an effective interventional approach.

Compliance with ethical standards

Conflict of interest The author declares that there is no conflict of interest.

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