Biohelikon: Cancer and Clinical Research 2014 2:a15

Editorial

The emerging role of glucose-6-phosphate dehydrogenase in cancer: a novel potential therapeutic target?

Manuela Polimeni[1*]

[1]Department of Oncology, University of Torino, via Santena 5 bis, 10126, Torino, Italy

[*] Email: manuela.polimeni@unito.it

Abstract

Cancer cells generally exhibit re-programming of their pathways. The expression of certain genes that directly control the rate of key metabolic pathways are drastically altered. Indeed, cancer cells show high rates of aerobic glycolysis (known as the Warburg effect) and an increase in pentose phosphate pathway activity due to the up-regulation of glucose-6-phosphate dehydrogenase (G6PD) in comparison to their non-transformed counterparts. These alterations are usually considered as an adaptation of tumor cells; however, they also contribute to the progression of tumor cells towards more aggressive phenotypes. Here we will discuss the critical role of G6PD in neoplastic transformation focusing on its potential utility as diagnostic marker as well as a novel potential therapeutic target.

Cancer cells exhibit quite abnormal behaviour by re-programming their metabolic pathways. In a normal cell, metabolism is balanced by at least three pathways (glycolysis, lipogenesis and the tricarboxylic acid cycle) closely linked to amino acid and nucleotide synthesis. However, cancer cells need higher rates of energy metabolism. Indeed, they consume large quantities of glucose and primarily use glycolysis for ATP production, even in the presence of adequate oxygen, thus directing glucose to biosynthesis and supporting their rapid growth and rate proliferation. It is increasingly evident that dysregulated expression of many genes involved in metabolic pathways can play direct roles in cancerogenesis and progression of tumor cells resulting in more aggressive phenotypes [1].

Among these pathways the pentose phosphate pathway (PPP), conventionally divided into an oxidative and a non oxidative branch, has been largely appreciated for its role as both a cellular source of ribose 5-phosphate for nucleotides biosynthesis, and reducing power to preserve redox homeostasis. Glucose-6-phosphate dehydrogenase (G6PD) is the first and rate-limiting enzyme of the oxidative branch [2]. G6PD is a key enzyme in the production of ribose-5-phosphate, which is essential for RNA and DNA synthesis in rapidly growing cells [3,4]. G6PD activity is also crucial in order to produce nicotinamide adenine dinucleotide phosphate (NADPH), which is an essential factor for glycolysis, contributing to fatty acid synthesis and to nucleotide synthesis [2]. The reducing power of NADPH is necessary as well to neutralize oxidative stress, for example to maintain the reduced form of glutathione which serves to detoxify free radicals and peroxides [5]. Therefore, G6PD is likely to contribute to cancer growth and survival by producing ribose and NADPH through PPP. Cancer cells generally show high rates of aerobic glycolysis (known as the Warburg effect) and an increase in PPP activity due to the up-regulation of G6PD in comparison to their non-transformed counterparts [6]. Increased G6PD mRNA and protein is a hallmark of many tumors [4,7,8]: in fact, elevated levels of expression and activity of G6PD are frequently observed in breast [9,10], colon [10], endometrial [11], cervical [12], prostatic [13], and lung cancers [14].

Interestingly, Kuo and colleagues demonstrate a causative role of G6PD in cell proliferation and neoplastic transformation, thus suggesting that G6PD may act as oncogene. The ectopic expression of G6PD in NIH 3T3 cells was shown to significantly increase intracellular levels of NADPH and GSH: G6PD-overexpressing cells are not contact inhibited, proliferate more rapidly, and exhibit anchorage-independent growth. Furthermore, these cells were shown to be tumorigenic as well as angiogenic in nude mice, in which injection with fibroblasts overexpressing G6PD can initiate neoplastic transformation [3,5]. Accumulating evidence indicates that the cellular redox state regulates various aspects of cellular function, including activation of transcription factors and carcinogenesis. Therefore, it is possible that changes in the intracellular redox status of G6PD-overexpressing cells may alter the activities of some transcriptional activators, which in turn regulate many target/effector genes or other cellular factors involved in cell proliferation and tumorigenesis.

It is now clear, many years after its discovery, that G6PD is a critical enzyme under complex regulatory control. The latest findings have elucidated G6PD regulation thus pointing out important interactions

with other proteins: the potential link with p53-family proteins strongly supports, in my opinion, its central role in cancer. The most frequently mutated gene in human tumors, the tumor suppressor p53, binds to G6PD preventing the formation of the active dimer thus suppressing glucose consumption, NADPH production and biosynthesis. Tumor-associated p53 mutants lack the G6PD-inhibitory activity: so, enhanced PPP glucose flux due to p53 inactivation may increase glucose consumption and direct glucose towards biosynthesis in tumor cells [15]. In addition, G6PD expression was elevated in various tumors, correlating with the up-regulation of TAp73. Indeed, TAp73 is a p53-related protein that is able to induce the expression of G6PD, thus improving cellular capability to withstand oxidative stresses and supporting proliferation. Jiang and colleagues discussed about the critical role of G6PD in TAp73-mediated cell proliferation: findings that strongly indicate that TAp73 may be a potential oncogene, and that G6PD is likely a focal point of regulation in oncogenic growth [16]. Moreover, recent work demonstrated a potential link between G6PD and patient survival rates and the co-expression of TAp63, another member of the p53 family that seems to play a central role in epithelial cancers [17].

Because of its role in the body's protection against oxidative stress and resistance/susceptibility to apoptosis, G6PD activity seems to be involved in tumor progression and therapy resistance. The higher rate of glycolysis in cancer cells generates an increased number of metabolites, such as hydrogen ions and lactate, that induce acidification of the cells by stimulating invasion, migration, mutagenesis, and radioresistance. The PPP supplies the cells with the NADPH that support antioxidant defenses. NADPH is the limiting substrate for the glutathione reductase (GSR), the enzyme that regenerates GSH from the oxidized glutathione (glutathione disulfide, GSSG), previously produced by the GSH peroxidase (GSHPx)-catalyzed reaction. So, NADPH generation and GSH recovery by G6PD may contribute to cancer cell survival by maintaining the intracellular pH and redox balance. Both carcinogenesis and MDR phenotype are frequently associated with an increased oxidative stress and activation of the cellular redox metabolism: indeed, GSH plays a pivotal role in cancer and multidrug resistance (MDR) development [18]. Several studies demonstrated an elevated PPP cycle, G6PD activity and cellular GSH in human MDR cells, supporting a significant correlation between PPP and MDR phenotype. Moreover, MDR is generally associated with both hypoxia, a common feature of many malignant tumors, and hypoxia-inducible factor-1, that can regulate *MDR1* and *G6PD* gene expression.

As a matter of fact, due to their critical role in tumorigenesis, G6PD could be considered a promising diagnostic tumoral biomarker and a potential target in cancer therapy. Indeed, G6PD overexpression could imply a neoplastic transformation or a more aggressive tumoral phenotype. To date, however, only a few G6PD inhibitors have been available. Buthionine S'R'-sulfoximine, a GSH depletion agent, is known to inhibit G6PD and is currently in phase I clinical trial. Another promising inhibitor of G6PD is 6-aminonicotinamide (6-AN), a $NADP^+$ analog that act as competitive inhibitor. Other G6PD inhibitors used in experimental work are the non-competitive ketosteroids epiandrosterone and dehydroepiandrosterone (DHEA). DHEA and 6-AN showed their efficacy in MDR reversion in a doxorubicin-resistant human colon cancer cell line (HT29-DX), which shows increased activity of G6PD and intracellular GSH content, and in doxorubicin-sensitive HT29 cells overexpressing G6PD [19]. Nevertheless, both classes of compounds that ubiquitously inhibit G6PD have disadvantages (e.g. the neurotoxicity for 6-AN and the lack of specificity for androsterone derivatives), so new pharmacological agents that could modulate G6PD activity with tissue- and enzyme-specific targeting are urgently required. Among natural products, catechin gallates and rosmarinic acid have been recently discovered and may represent the next generation of PPP inhibitors. Recently, a high-throughput screening assay to identify novel human G6PD inhibitors has revealed new compounds that presented ≥50% G6PD inhibition with IC(50) values of <4 μM. Compared with the known G6PD inhibitors DHEA and 6-AN, the newly identified inhibitors were 100- to 1000-fold more potent [20]. Reducing G6PD activity may be an efficient way to inhibit or decelerate cancer growth in order to prevent development, control its evolution and overcome drug resistance. Therein, in my opinion, new efforts in this research field are mandatory: development or design of potent and selective G6PD inhibitors would provide novel opportunity for cancer therapy increasing the ratio between therapeutic benefits and side effects.

References

1. Furuta E, Okuda H, Kobayashi A, Watabe K (2010). Metabolic genes in cancer: their roles in tumor progression and clinical implications. *Biochim Biophys Acta*, 1805(2): 141-152.
2. Stanton RC (2012). Glucose-6-phosphate dehydrogenase, NADPH, and cell survival. *IUBMB Life*, 64(5): 362-369.
3. Kuo W, Lin J, Tang TK (2000). Human glucose-6-phosphate dehydrogenase (G6PD) gene transforms NIH 3T3 cells and induces tumors in nude mice. *Int J Cancer*, 85(6): 857-864.
4. Boros LG, Brandes JL, Yusuf FI, Cascante M, Williams RD, *et al.* (1998). Inhibition of the oxidative and nonoxidative pentose phosphate pathways by somatostatin: a possible mechanism of antitumor action. *Med Hypotheses*, 50(6): 501-506.
5. Kuo WY, Tang TK (1998). Effects of G6PD overexpression in NIH3T3 cells treated with tert-butyl hydroperoxide or paraquat. *Free Radic Biol Med*, 24(7-8): 1130-8.
6. Zhang C, Zhang Z, Zhu Y, Qin S (2014). Glucose-6-phosphate dehydrogenase: a biomarker and potential therapeutic target for cancer. *Anticancer Agents Med Chem*, 14(2): 280-289.
7. Frederiks WM, Bosch KS, Hoeben KA, van Marle J, Langbein S (2010). Renal cell carcinoma and oxidative stress: The lack of peroxisomes. *Acta Histochem*, 112(4): 364-371.
8. Frederiks WM, Vizan P, Bosch KS, Vreeling-Sindel?rov? H, Boren J, *et al.* (2008). Elevated activity of the oxidative and non-oxidative pentose phosphate pathway in (pre)neoplastic lesions in rat liver. *Int J Exp Pathol*, 89(4): 232-240.
9. Bokun R, Bakotin J, Milasinović D (1987). Semiquantitative cytochemical estimation of glucose-6-phosphate dehydrogenase

activity in benign diseases and carcinoma of the breast. *Acta Cytol*, 31(3): 249-252.
10. Koudstaal J, Makkink B, Overdiep SH (1975). Enzyme histochemical pattern in human tumours. II. Oxidoreductases in carcinoma of the colon and the breast *Eur J Cancer*, 11: 111-115.
11. Hughes EC (1976). The effect of enzymes upon metabolism, storage, and release of carbohydrates in normal and abnormal endometria. *Cancer*, 38(1 SUPPL): 487-502.
12. Duţu R, Nedelea M, Veluda G, Burculeţ V (1980). Cytoenzymologic investigations on carcinomas of the cervix uteri. *Acta Cytol*, 24(2): 160-166.
13. Zampella EJ, Bradley EL Jr, Pretlow TG nd (1982). Glucose-6-phosphate dehydrogenase: a possible clinical indicator for prostatic carcinoma. *Cancer*, 49(2): 384-387.
14. Dess? S, Batetta B, Cherchi R, Onnis R, Pisano M, *et al.* (1988). Hexose monophosphate shunt enzymes in lung tumors from normal and glucose-6-phosphate-dehydrogenase-deficient subjects. *Oncology*, 45(4): 287-291.
15. Jiang P, Du W, Wang X, Mancuso A, Gao X, *et al.* (2011). p53 regulates biosynthesis through direct inactivation of glucose-6-phosphate dehydrogenase. *Nat Cell Biol*, 13(3): 310-316.
16. Jiang P, Du W, Yang X (2013). A critical role of glucose-6-phosphate dehydrogenase in TAp73-mediated cell proliferation. *Cell Cycle*, 12(24): 3720-3726.
17. D'Alessandro A, Amelio I2, Berkers CR3, Antonov A2, Vousden KH4, *et al.* (2014). Metabolic effect of TAp63α: enhanced glycolysis and pentose phosphate pathway, resulting in increased antioxidant defense. *Oncotarget*, 5(17): 7722-7733.
18. Kuo MT (2009). Redox regulation of multidrug resistance in cancer chemotherapy: molecular mechanisms and therapeutic opportunities. *Antioxid Redox Signal*, 11(1): 99-133.
19. Polimeni M, Voena C, Kopecka J, Riganti C, Pescarmona G, *et al.* (2011). Modulation of doxorubicin resistance by the glucose-6-phosphate dehydrogenase activity. *Biochem J*, 439(1): 141-149.
20. Preuss J, Richardson AD, Pinkerton A, Hedrick M, Sergienko E, *et al.* (2013). Identification and characterization of novel human glucose-6-phosphate dehydrogenase inhibitors. *J Biomol Screen*, 18(3): 286-297.