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Review Article

The pentose phosphate pathway: An antioxidant defense and a crossroad in tumor cell fate

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ABSTRACT

The pentose phosphate pathway, one of the main antioxidant cellular defense systems, has been related for a long time almost exclusively to its role as a provider of reducing power and ribose phosphate to the cell. In addition to this "traditional" correlation, in the past years multiple roles have emerged for this metabolic cascade, involving the cell cycle, apoptosis, differentiation, motility, angiogenesis, and the response to anti-tumor therapy. These findings make the pentose phosphate pathway a very interesting target in tumor cells. This review summarizes the latest discoveries relating the activity of the pentose phosphate pathway to various aspects of tumor metabolism, such as cell proliferation and death, tissue invasion, angiogenesis, and resistance to therapy, and discusses the possibility that drugs modulating the pathway could be used as potential tools in tumor therapy.

Contents

Abbreviations: PPP, pentose phosphate pathway; GSH, reduced glutathione; G6PD, glucose-6-phosphate dehydrogenase; 6PGD, 6-phosphogluconic dehydrogenase; TA, transaldolase; GSR, glutathione reductase; GSSG, oxidized glutathione; GSHPx, glutathione peroxidase; ROS, reactive oxygen species; NF-κB, nuclear factor-κB; HIF-1α, hypoxia-inducible factor-1α; 6-AN, 6-aminonicotinamide; DHEA, dehydroepiandrosterone; TK, transketolase; TKTL, transketolase-like proteins; NOX, NADPH oxidase; NOS, nitric oxide synthase; OT, oxythiamine; Hsp, heat shock protein; TIGAR, TP53-induced glycolysis and apoptosis regulator; VEGF, vascular endothelial growth factor; eNOS, endothelial NOS; SOD, superoxide dismutase; MDR, multidrug resistance; ADM, adriamycin; MRP, multidrug-resistance-related protein

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The pentose phosphate pathway: an overview

The history of the metabolic role of the pentose phosphate pathway (PPP), also known as the hexose monophosphate shunt, began in 1926, when the introduction of new antimalarial drugs, such as primaquine, led to the first medical description of a drug-induced hemolytic anemia correlated with an intrinsic defect of red blood cell metabolism [1]. In primaquine-sensitive red blood cells the formation of Heinz bodies and the disappearance of reduced glutathione (GSH) in the presence of the oxidant agent acetylphenylhydrazine [2] were related to a deficiency of the first enzyme of PPP, glucose-6-phosphate dehydrogenase (G6PD; EC 1.1.1.49) [3]. Since these first observations, the number of drugs inducing hemolysis, the spectrum of clinical presentations, and the variety of genetic defects affecting G6PD have constantly increased [4], and in parallel the PPP appeared to be not only a shunt pathway in the metabolism of hexose monophosphate, but also a critical pathway in cell redox balance and proliferative fate.

The percentage of glucose metabolized by PPP may vary from 5 to 30%, in a tissue-dependent manner. The flux through PPP reaches the maximal percentage in lipid- and steroid-synthesizing tissues (such as liver, white adipose tissue, lactating mammary glands, adrenal glands, and gonads) and in red blood cells. In all cells, however, the basal rate of PPP may widely vary, depending on the amount of $NADP^+$ and other cell conditions (exposure to oxidizing agents, proliferative activity, etc.) modifying the $NADP^+$/NADPH ratio [5]. In vivo many PPP enzymes, including G6PD, 6-phosphogluconic dehydrogenase (6PGD; EC 1.1.1.43), and transaldolase (TA; EC 2.2.1.2), are aggregated in complexes located near the glucose transporter; in this way, glucose flux through the PPP is regulated more efficiently [6]. Given the central role of PPP as a source of nucleic acid precursor and reducing equivalents, it is not surprising that some steps of PPP have been conserved through evolution. In plants, for instance, the enzymes of the oxidative PPP have been localized in cytosol and plastids [7]. A metabolic flux similar to the PPP has been detected in bacteria colonizing the gastrointestinal epithelia [8]. PPP is conventionally divided into an oxidative and a nonoxidative branch and the activity of the former is generally higher than the activity of the latter [9].

The oxidative branch of the PPP and its regulation in mammalian cells

In the oxidative branch, glucose 6-phosphate is oxidized into 6-phosphogluconolactone by G6PD, which produces NADPH with a 1:1 stoichiometry; the unstable lactone ring is opened by lactonase into 6-phosphogluconic acid and undergoes an oxidative decarboxylation by the 6PGD enzyme, which produces a second NADPH and CO_2. The resulting ribulose 5-phosphate can be then converted into ribose 5-phosphate and used for the synthesis of nucleotides (Fig. 1). Rapidly dividing cells have high needs for pentose phosphates; this demand is particularly high for cancer cells, in which the PPP provides about 85% of pentoses incorporated into DNA [10]. Thus, the first condition that strongly affects PPP activity is the rate of cell proliferation: the greater is the proliferation, the greater is the requirement for ribose 5-phosphate and NADPH for nucleic acid synthesis and then the glucose flux into the PPP. The second condition that is critical for

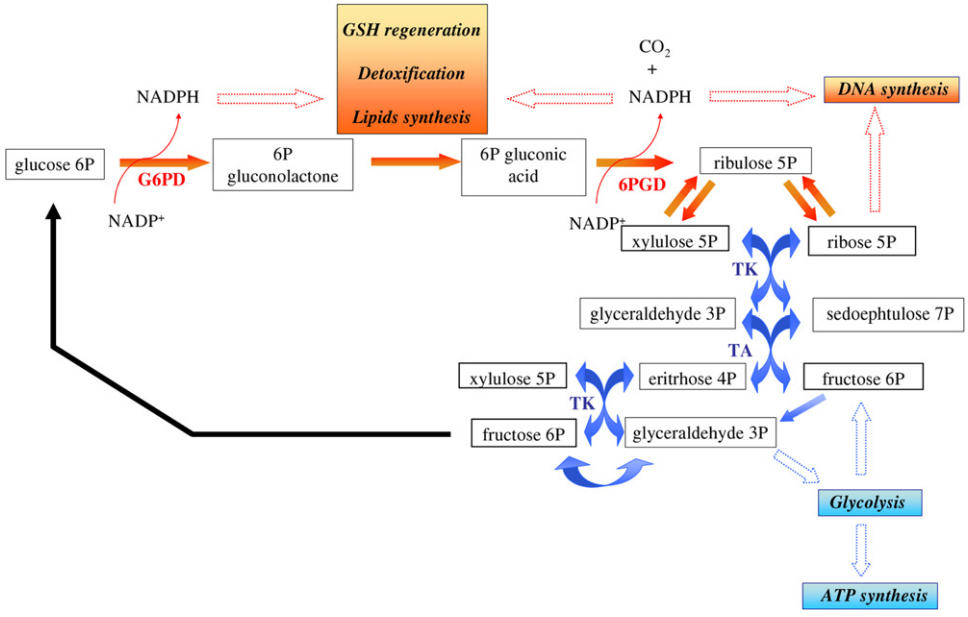

Fig. 1. Schematic representation of the oxidative and nonoxidative branches of the pentose phosphate pathway. In the oxidative branch of the pentose phosphate pathway (red arrows) glucose 6-phosphate is oxidized and decarboxylated into ribulose 5-phosphate. This is then isomerized into ribose 5-phosphate, an essential component of nucleotides. Two moles of NADPH per mole of glucose 6-phosphate entering the pentose phosphate pathway are also produced and provide reducing equivalents for the regeneration of GSH via glutathione reductase, the synthesis of fatty acids and sterols, the detoxification of xenobiotics, and the synthesis of DNA. In the nonoxidative branch (blue arrows), pentose phosphate undergoes two-carbon and three-carbon exchange reversible reactions, finally yielding fructose 6-phosphate and glyceraldehyde 3-phosphate, which can enter the glycolytic pathway, being reconverted into glucose 6-phosphate or further oxidized to meet the cellular ATP demands. P, phosphate; G6PD, glucose-6-phosphate dehydrogenase; 6PGD, 6-phosphogluconate dehydrogenase; GSH, reduced glutathione; TK, transketolase; TA, transaldolase. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)