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The Pentose Phosphate Pathway in Cancer: Regulation and Therapeutic Opportunities

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Abstract
Background: Tumorigenesis is associated with deregulation of nutritional requirements, intermediary metabolites production, and microenvironment interactions. Unlike their normal cell counterparts, tumor cells rely on aerobic glycolysis, through the Warburg effect. ***Summary:*** The pentose phosphate pathway (PPP) is a major glucose metabolic shunt that is upregulated in cancer cells. The PPP comprises an oxidative and a nonoxidative phase and is essential for nucleotide synthesis of rapidly dividing cells. The PPP also generates nicotinamide adenine dinucleotide phosphate, which is required for reductive metabolism and to counteract oxidative stress in tumor cells. This article reviews the regulation of the PPP and discusses inhibitors that target its main pathways. ***Key Message:*** Exploiting the metabolic vulnerability of the PPP offers potential novel therapeutic opportunities and improves patients' response to cancer therapy.

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Introduction

Cancer cells alter their metabolism in order to sustain their rapid proliferation and survival [1]. The hallmarks of cancer highlight the complexity of the multistep process of tumorigenesis [2, 3] that includes both genetic and epigenetic alterations [4]. Cancer hallmarks include enhanced proliferative signaling, evading programmed cell death, avoidance of growth suppressors, unlimited replicative potential, induction of angiogenesis, tissue invasion and metastasis, escaping immune destruction, and reprograming cellular metabolism and bioenergetics [2]. Targeting cancer metabolism has gained interest over the past decade [5]. Indeed, the higher rates of energy demand in cancer cells involve the alteration of protein, lipid, carbohydrate, and nucleic acid metabolism. In addition, the abnormal tumor microenvironment induces stressors such as hypoxia, low pH, and nutrient deprivation that elicit cancer metabolism alteration [6]. The uncontrolled proliferation of cancer cells requires an increased import of building blocks to support tumor progression. Glucose and glutamine, the principal growth-supportive substrates, provide intermediates that are diverted into branching pathways that fuel adenosine triphosphate (ATP), nicotinamide adenine dinucleotide

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(NADH), and nicotinamide adenine dinucleotide phosphate (NADPH) production [7, 8]. These molecules are essential for nucleotide and nonessential amino acids assembly as well as for fatty acid and organelle biosynthesis [9]. Cancer cells rewire their metabolism and rely on high rates of aerobic glycolysis to meet their extra growth and maintenance requirements [10].

The pentose phosphate pathway (PPP) is the first among a series of pathways that branch from glycolysis. The PPP is a major glucose catabolic and reducing anabolic pathway essential for neoplastic transformation due to the production of NADPH and nucleic acid precursors [11]. Besides upregulating the PPP, tumor cells aberrantly activate oncogenes and/or repress tumor suppressor genes that lock cancer cells in a constitutively scavenging state. Notably, the Ras and the phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin signaling pathways induce the overexpression of the plasma membrane glucose transporter 1 (GLUT1) and hexokinase, which is the first enzyme of glycolysis [12]. This marked increase in glucose consumption by tumors compared to healthy counterpart tissue is known as the Warburg effect, where the majority of glucose is transformed into lactate [13]. Otto Warburg reported that in most cancer cells, even in the presence of oxygen, tumor cells favor and reprogram their glucose metabolism to rely largely on glycolysis for energy production, resulting in a state of "aerobic glycolysis" [14]. However, under aerobic environment, normal cells process glucose via glycolysis into pyruvate that is further metabolized in the mitochondria into carbon dioxide, ATP, and water. Although there are several metabolic pathways that are deregulated in cancer [15], this review focuses on the involvement of the PPP in cancer cell proliferation and survival, and its inhibition in cancer therapeutics.

The Pentose Phosphate Pathway: Oxidative and Nonoxidative Phases

The PPP, also known as the hexose monophosphate shunt or the phosphogluconate pathway, is a pivotal pathway that is induced in neoplasms [16]. The PPP contributes to ribonucleotide synthesis and maintains cytosolic reduction-oxidation (redox) balance through NADPH production. Depending on cellular metabolic needs, the PPP may utilize intermediates from the tricarboxylic acid, lipid, and amino acid metabolic pathways. The first PPP enzyme, glucose-6-phosphate dehydrogenase (G6PD), gained significant interest for its involvement in hemolytic anemia, a condition induced by oxidizing agents, such as fava beans. Moreover, red blood cells are rendered vulnerable to oxidative stress in patients with G6PD deficiency as the PPP is their unique source of NADPH and plays a major antioxidant role by scavenging reactive oxygen species (ROS) [17]. With over 400 million people suffering from genetic defects in G6PD, it is interesting to study its correlation with a lower risk of cancer as G6PD may act as an oncogene in cancer cells [18].

The PPP is composed of 2 phases: the irreversible oxidative and the reversible nonoxidative (shown in Fig. 1). The oxidative phase involves 3 enzymatic reactions that generate 2 NADPH molecules and ribulose-5-phosphate (Ru5P). The first substrate, glucose-6-phosphate, is oxidized to 6-phosphogluconate (6 PG) by G6PD, yielding the first NADPH molecule. Subsequently, 6 PG undergoes oxidative decarboxylation by 6-phosphogluconate dehydrogenase (6PGD) producing Ru5P and the second NADPH molecule. G6PD catalyzes the rate determining step in the oxidative phase, highlighting its firmly regulated activity. In rapidly proliferating cells, a high $NADP^+$/NADPH ratio positively modulates the activity of G6PD to support NADPH production. NADPH is an essential anabolic reducing agent that supports reductive biosynthesis of fatty acids and nucleotides. Furthermore, NADPH maintains cell survival under oxidative stress conditions that are generated from deregulated mitochondria or metabolically active cells [19]. Glutathione (GSH) is an essential antioxidant tripeptide that scavenges ROS, and NADPH is a critical cofactor involved in continuously replenishing the GSH pool [20]. Enhanced G6PD activity was reported in papillary thyroid carcinoma [21], colorectal [22], renal [23], and prostate cancer [24]. In fact, G6PD activity is upregulated by several oncogenes, such as platelet-derived growth factor, epidermal growth factor, phosphoinositide 3-kinase, and Ras [25, 26]. On the other hand, p53 was reported to be a negative modulator of G6PD by binding directly to it and preventing monomer dimerization and enzyme activation [27]. 6PGD has also been frequently studied with G6PD for its pivotal role in tumorigenesis. In fact, genetic silencing of 6PGD led to the accumulation of cellular p53 proteins, resulted in senescence of lung cancer cells, and slowed tumor growth in mouse xenograft models [28].

The reversible nonoxidative phase starts with Ru5P that is transformed into ribose-5-phosphate (R5P) by ribulose-5-phosphate isomerase. R5P is an essential component of purine and pyrimidine nucleotides biosynthesis. Ru5P may also be converted into xylulose-5-phosphate by ribulose-5-phosphate-3-epimerase, which was reported to enhance glycolytic flux [17]. The nonoxida-

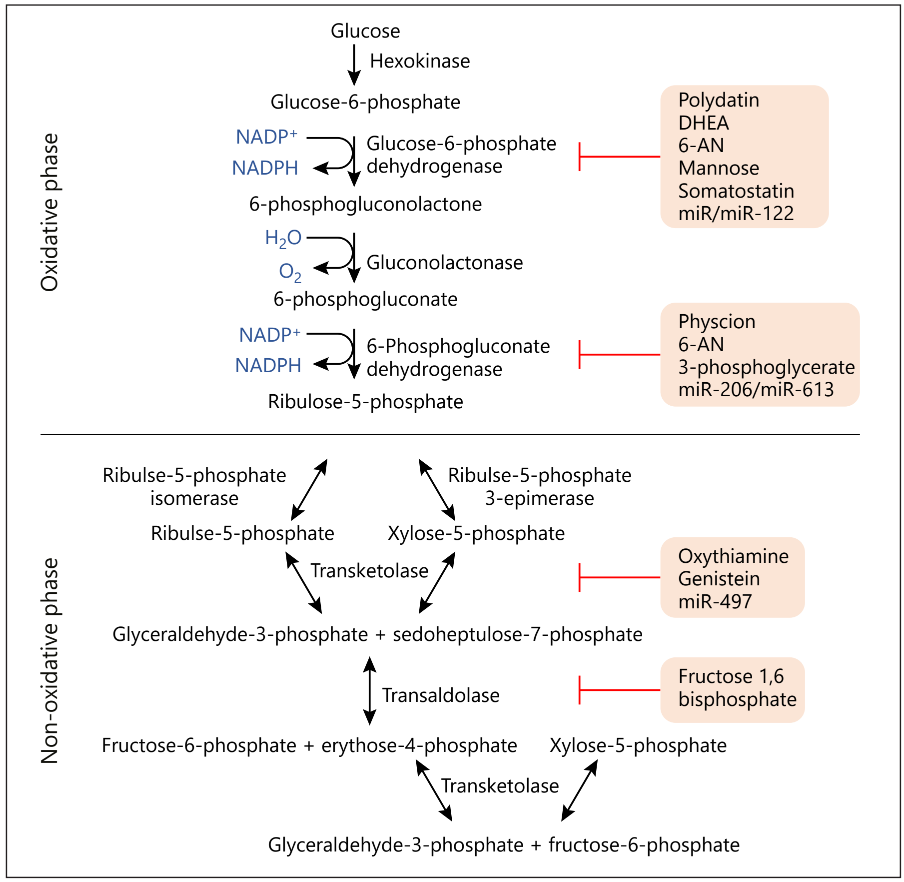

Fig. 1. Schematic representation of the oxidative and nonoxidative phases of the PPP as well as various inhibitors of specific enzymes that may be targeted in cancer treatments as covered in this review. 6-AN, 6-aminonicotinamide; DHEA, dehydroepiandrosterone; miRNA, microRNA; 6PGD, 6-phosphogluconate dehydrogenase; G6PD, glucose-6-phosphate dehydrogenase; PPP, pentose phosphate pathway; TKT, transketolase; TALDO, transaldolase; G6P, glucose-6-phosphate; Ru5P, ribulose-5-phosphate; 6 PG, 6-phosphogluconate; RPI, ribulose-5-phosphate isomerase; RPE, ribulose-5-phosphate-3-epimerase; F6P, fructose-6-phosphate; G3P, glyceraldehyde-3-phosphate; NADPH, nicotinamide adenine dinucleotide phosphate.

tive PPP phase is controlled by transketolase (TKT) and transaldolase (TALDO). The reversible nature of these enzymes allows glycolytic metabolites, such as fructose-6-phosphate (F6P) and glyceraldehyde-3-phosphate (G3P), to be recruited into this pathway and vice versa. It has been reported that the nonoxidative PPP enzymes are upregulated in cancer [11]. In a pancreatic cancer mouse model, K-Ras stimulation was shown to activate the nonoxidative phase of the PPP [29]. TKT overexpression in lung, prostate, and breast cancer cells has been correlated with tumor invasiveness and poor cancer prognosis [17, 30]. TALDO has been shown to be elevated in several tumors, such as squamous cell carcinomas [31] and hepatocellular carcinoma [32].

Regulation of the Pentose Phosphate Pathway

The PPP enzymes can be allosterically regulated by their own metabolic products to modulate enzymatic activity and facilitate cellular growth. Depending on cellular needs and environmental cues, the PPP can operate in different modes. In rapidly dividing cells, TKT and TALDO reversely channel G3P and F6P from glycolysis to the nonoxidative PPP to generate RNA and DNA precursors from R5P. During oxidative stress, hexose phosphate isomerase converts F6P into G6P through glycolysis and shuttles it back to the PPP to maintain NADPH homeostasis. Similarly, under high ATP demand, the PPP products can be reshuffled into the glycolytic pathway [33]. When glucose availability is scarce, pathways other than the PPP maintain NADPH thresholds which are essential to mitigate oxidative stress and prevent cell death. One of these pathways is mediated by the activation of AMP-activated protein kinase that halts the consumption of NADPH by fatty acid synthesis. Simultaneously, the malic enzyme and the cytosolic isocitrate dehydrogenase induce fatty acid oxidation which generates more NADPH molecules [17]. In colorectal cancer, an increase in $NADP^+$ content due to the loss of G6PD activity is compensated by an upregulation in malic and isocitrate dehydrogenase enzymes flux to maintain a high NADPH/

NADP+ ratio [34]. In many cancers, several factors are involved in positively regulating the flux into the PPP, namely, the proapoptotic Phorbol-12-myristate-13-acetate-induced protein 1, also known as NOXA. Interestingly, NOXA had a dual function. In the presence of glucose, NOXA facilitates the usage of the PPP to promote survival, while under scarce glucose conditions, NOXA is dephosphorylated which functions as a proapoptotic protein [35].

PPP Impact on Cancer Metabolism

Cancer cells can overcome the strict metabolic surveillance of the PPP by acquiring genetic mutations and epigenetic modifications that modulate its activity [36]. For instance, the tumor suppressor p53 stimulates the flux through glycolysis and upregulates the expression of the apoptosis regulator (TP53-inducible glycolysis and apoptosis regulator). TP53-inducible glycolysis and apoptosis regulator functions as a fructose-2, 6-bisphosphatase, thus inhibiting phosphofructokinase 1 activity, thereby redirecting glycolytic intermediates toward the PPP [37]. p53 is also known to suppress the transcription of glucose transporters GLUT1 and GLUT4. On the other hand, p21-activated kinase 4 promotes glucose uptake, NADPH production, and lipid biosynthesis. p21-activated kinase 4 is positively correlated with colorectal cancer in tissue samples, where it was shown to bind to G6PD and enhance its activity [38]. Similarly, mammalian target of rapamycin complex 1 is frequently activated in cancer cells. Its activation is often associated with a substantial upregulation in the oxidative phase of the PPP, involving particularly G6PD, by increasing the activity of the transcription factor sterol regulatory element-binding protein [39].

The activity of the PPP oxidative phase enzymes is upregulated in colorectal cancer [40] (unpublished data). 6PGD expression level and enzymatic activity are elevated in malignant hepatocellular carcinoma cells compared to normal hepatocytes [41]. Furthermore, the amount of G6PD and TKT enzymes is elevated in colorectal cancer and hepatocellular carcinoma patient tissues compared to normal counterparts [40, 42]. Thus, exploiting the reprogrammed metabolism in tumor cells may offer novel therapeutic targets against cancer [9, 43]. We will next cover the use of PPP inhibitors as a therapeutic window in cancer cells.

PPP Inhibitors

The PPP inhibitors can be divided into the oxidative phase or the nonoxidative phase inhibitors (Table 1).

Oxidative Phase Inhibitors

Increased flux through the PPP is observed in neoplasia and tumor invasion, and its inhibition remains a plausible attractive therapeutic approach against many cancers. Unfortunately, efficient anti-PPP agents are not available in the clinic and further investigations are still needed [44]. Listed below are a set of synthetic and natural oxidative phase inhibitors of the PPP, namely, inhibitors of G6PD and 6PGD that could be used to treat cancer and restore sensitivity to chemotherapy (Table 1). In fact, enhanced-PPP activity has been shown to be implicated in cisplatin resistance in solid tumors [45].

G6PD Inhibitors

G6PD has gained significant attention among the scientific community for its broad implications in health and disease [46]. Indeed, G6PD overexpression and elevated activity have been associated with many types of cancers. Here, we emphasize the main G6PD inhibitors in preclinical and clinical development as well as in the clinic for use as anticancer agents.

Polydatin

Polydatin (3,4′,5-trihydroxystilbene-3-β-d-glucoside; trans-resveratrol 3-β-mono-D-glucoside; piceid) is a glucoside of resveratrol extract from the Chinese herb *Polygonum cuspidatum* [47]. Polydatin is abundantly present in plants such as peanuts, grapes, and cocoa-containing foods. Polydatin has many important biomedical properties, such as cardioprotective activity [48], anti-inflammatory [49], immunomodulatory [50], and antioxidant effects [51]. Additionally, it has apoptotic characteristics in neoplastic cells by directly inhibiting the activity of G6PD and impairing NADPH production. In head and neck squamous cell carcinoma cells, polydatin was shown to increase ROS production, endoplasmic reticulum stress, and apoptosis while inducing cell cycle arrest and inhibiting invasion [44]. In an orthotopic metastatic tongue cancer model, polydatin led to tumor regression and repressed lymph node metastasis [44]. Moreover, polydatin revealed a synergistic effect with lapatinib, a tyrosine kinase inhibitor, in breast cancer cells, by inducing autophagy [52]. In colorectal cancer, polydatin was shown to induce cell-specific differentiation and apoptosis [53]. Currently, polydatin is in phase II clinical trials and pre-

Table 1. Comparison between different oxidative and nonoxidative PPP inhibitors

Enzyme	Drugs	Nature of the drugs	Mechanism of action	Phase in clinics
Oxidative PPP inhibitors				
G6PD	Polydatin	Glucoside of resveratrol	Natural inhibitor	Phase II clinical trials [52]
	DHEA	Steroid hormone	Noncompetitive inhibitor	In the clinic [137]
	6-AN	Monocarboxylic acid amide	Competitive inhibitor	In the clinic [138]
	Mannose	Carbohydrate and monosaccharide	Unknown	Preclinical development [78, 79]
	Somatostatin	Peptide hormone	Unknown	In the clinic [139]
	miR-1 and miR-122	microRNA; a type of noncoding RNA	Post-transcriptional repression of 3′-UTR *g6pd* mRNA	miR-1: preclinical development [140–142] miR-122: Phase II clinical trials [143]
6PGD	Physcion	Anthraquinone derivative	Hydrophobic interaction with 6PGD at Met15 site	Preclinical development [144]
	6-AN	Monocarboxylic acid amide	Competitive inhibitor	In the clinic [138]
	3-PG	Monophosphoglyceric acid; intermediate of glycolysis	Competitive inhibitor	Preclinical development [95]
	miR-206 and miR-613	miRNA	Post-transcriptional repression of 3′-UTR *6PGD* mRNA	Preclinical development [96, 145]
Nonoxidative PPP inhibitors				
TKT	Oxythiamine	Thiamine analog	Noncompetitive irreversible inhibitor	Preclinical development [146]
	Genistein	Isoflavonoid derivative of soy plant	Unknown	Phase II clinical trials [147]
	miR-497	miR	Post-transcriptional repression of 3′-UTR *TKT* mRNA	Preclinical development [148, 149]
TALDO	Fructose 1,6-bisphosphate	Monosaccharide intermediate of glycolysis	Competitive and noncompetitive inhibition	In the clinic [150]

6-AN, 6-aminonicotinamide; 6PGD, 6-phosphogluconate dehydrogenase; DHEA, dehydroepiandrosterone; G6PD, glucose-6-phosphate dehydrogenase; PPP, pentose phosphate pathway; TKT, transketolase; TALDO, transaldolase; 3-PG, 3-phosphoglycerate; miR, microRNA.

liminary data show minimal side effects and high tolerance in humans, making it a natural favorable treatment [54]. However, the definitive target proteins and mode of action of polydatin remain to be elucidated.

Dehydroepiandrosterone

In 1939, the discovery of the metabolic pathway of dehydroepiandrosterone (DHEA) was awarded the Nobel Prize in Chemistry [55]. DHEA (3β-hydroxy-5-androsten-17-one) is a 19-carbon endogenous hormone synthesized de novo from cholesterol in the adrenal gland. This steroid is a precursor for estrogen and androgen [56]. Together with its sulfur ester DHEA-S, they represent the most abundant steroid in the body and peak during the second and third decades of life [55]. However, DHEA is a much more potent G6PD inhibitor than DHEA-S [56, 57]. DHEA was originally found to have a chondroprotective role and to be effective against osteoarthritis. DHEA exerts a beneficial effect on osteoarthritic cartilage by favoring anabolic versus catabolic signaling pathways. For instance, DHEA upregulates the expression of the tissue inhibitor of metalloproteinases-1, while it prevents the expression and protein synthesis of metalloproteinases-1 [58]. DHEA was also found to suppress pro-inflammatory cytokines and to inhibit atherosclerosis [59]. Moreover, epidemiological analysis has shown an inversely proportional correlation between serum DHEA levels and risk of developing breast hyperplasia [60].

Besides its natural role as a hormone, research data suggest that DHEA is a strong inhibitor of mammalian G6PD [19]. The exact nature of DHEA inhibition mechanism is not yet elucidated. Some studies have shown that DHEA behave as an uncompetitive inhibitor while other studies show that DHEA may act as a noncompetitive G6PD inhibitor. It has been described that DHEA decreases cellular NADPH and increases ROS levels [61]. Moreover, many studies have indicated that DHEA was able to reduce thyroid and colorectal cancer cell proliferation [19, 62]. It should however be noted that DHEA is rapidly converted into other steroid hormones which raise concerns about its potential efficacy as an inhibitor of the oxidative phase of the PPP [56]. Clinical trials using DHEA are burdened by the elevated oral doses required. Therefore, DHEA analogs are still to be developed for a better bioavailability.

6-Aminonicotinamide

6-Aminonicotinamide (6-AN) is a monocarboxylic acid amide that is the most potent antagonist of niacin. This metabolite is converted, into its active form in vivo, resulting in analogs of NAD^+ and $NADP^+$, with the latter being further completely modified into 6-AN adenine dinucleotide phosphate at much faster rate than NAD^+ [63]. These analogs are incapable of participating as coenzymes in the redox reactions of human metabolism [64]. Conversion of NAD^+ and $NADP^+$ into their corresponding AN analogs involves substituting the nicotinamide moiety of existing NAD^+ and $NADP^+$ by AN or incorporating AN during the de novo synthesis of the pyridine nucleotides [65].

6-AN acts as a competitive inhibitor of the $NADP^+$-dependent G6PD and 6PGD enzymes, evidenced by 6-AN increasing the levels of ROS production while reducing NADPH biosynthesis [66]. The incubation of 6-AN with isolated hepatocytes [64] and human lung carcinoma cells [67] resulted in a marked buildup of 6 PG levels. Preclinical trials have shown that the application of 6-AN in adjuvant antineoplastic drugs potentiates the effects of radiation and chemotherapy [68], as reported in mammary carcinoma mouse models [19]. 6-AN hindered the growth of a panel of thyroid cancer cells [62]. Interestingly, 6-AN increased the expression of the glucose-regulated stress protein GRP78 and was correlated with enhanced response to DNA cross-linking agents in colorectal cancer [69]. Notably, the combination of cisplatin and 6-AN resulted in accumulation in platinum-DNA adducts [66]. Combining 6-AN with other drugs sensitizes treatment in distinct cancers such as breast, ovarian, leukemia [70], and hepatocarcinoma [71]. In colorectal cancer, 6-AN reversed the observed increased G6PD activity. It also repressed the multidrug resistance of doxorubicin-resistant human colon cancer cells [72].

6-AN displays cytotoxic and high antiviral activity, as evidenced in several cell lines and transgenic-hepatitis B virus mouse models. 6-AN inhibited the secretion of hepatitis B virus surface antigen in hepatoblastoma cells through a reduction in the peroxisome proliferators-activated receptor-α transcription factor activity. Previous studies have demonstrated the implication of 6-AN in treating skin diseases, namely, psoriasis. 6-AN has also shown antiparasitic responses against *Leishmania* and *Plasmodium falciparum* [73]. The use of 6-AN in the clinic is hindered by its toxicity at elevated concentrations, serious side effects, such as B-complex vitamin deficiency, serious neurological damage, and paralysis presumably due to its direct action on the central nervous system [74]. Further clinical research is undergoing to determine the effective doses of 6-AN to be administered to patients.

Mannose

Mannose (D-mannose) is a natural C-2 epimer of glucose imported by GLUT1 transporter [75]. Inside the cell, hexokinase phosphorylates mannose to produce mannose-6-phosphate (M6P). The latter is either isomerized by phosphomannose isomerase (PMI) into F6P, or engaged into N-glycosylation via phosphomannosemutase 2, or catabolized by DN-9-phosphate synthase for the synthesis of 2-keto-3-deoxy-D-glycero-D-galacto-nononic acid [76]. The fate of M6P depends on the cellular ratio of PMI to phosphomannosemutase 2. A higher ratio stimulates catabolism, while a lower ratio leads to M6P accumulation, which interferes with glucose metabolism. However, mannose slightly contributes to cellular bioenergetics as the physiological concentration of mannose in human blood is one-hundredth of that of glucose [75].

Mannose has recently captured the interest of researchers for its anticancer effect via glucose metabolism impediment [77, 78]. Mannose showed potential anticancer effects by suppressing growth, inducing G_0/G_1 cell cycle arrest, promoting cisplatin-induced apoptosis, and reducing cell invasiveness in lung cancer [79]. Gonzalez et al. [78] demonstrated that mannose did not affect the intracellular levels of glucose. However, mannose was poorly metabolized inside the cell and affected several metabolic pathways. The intracellular accumulation of mannose as M6P inhibits 3 enzymes that facilitate glucose metabolism, namely, hexokinases, phosphoglucose isomerase, and G6PD [78].

Mannose showed synergistic interaction with chemotherapeutic drugs, such as cisplatin and doxorubicin, and increased their cytotoxic effect through potentiating intrinsic apoptotic pathways [78]. Therefore, mannose was suggested to be used clinically in combination with conventional chemotherapeutics agents [78, 79].

Intracellular PMI levels dictate the response to mannose. High levels of PMI are associated with mannose-insensitive cells while depletion of PMI by RNA interference restores sensitivity to mannose [78]. Moreover, PMI overexpression eliminates the impact of mannose on glucose consumption. Notably, PMI levels varied in human tumors, which could be used as a biomarker for mannose sensitivity (unpublished data). Mannose alone or in combination with conventional cancer therapies can be used as a potential new anticancer treatment to modulate glucose metabolism in cancer cells.

Mannose receptors (MRs) are overexpressed on many cancerous cells [80]. Recently, mannose was highlighted as an anticancer drug-delivery system, which can carry chemotherapeutics to target tissues while avoiding off-target tissues, thus minimizing side effects. Therefore, encapsulating anticancer drugs into a mannose-therapeutic system can potentially target tumors through MR-mediated endocytosis to enhance the beneficial effect while reducing toxicity [81]. Moreover, MR was found to be expressed on the surface of dendritic cells and macrophages; thus, it can be targeted to induce anticancer response and stimulate immunotherapy [80].

Somatostatin

Somatostatin is a steroid peptide hormone secreted from the hypothalamic and central nervous system regions of the human body. Although somatostatin's main function is to suppress the release of growth factor hormones, it is involved in pathophysiological and cancer-related changes in the body [82]. Somatostatin has been documented to play antitumor effects in several animal models and human cancers cell lines and to cause glucose intolerance through G6PD suppression and TKT-catalyzed reactions in tumors [83]. Deane and Woo [83] showed that administration of somatostatin significantly inhibited G6PD gene transcription and G6PD enzymatic activity in sea urchins by 70 and 52%, respectively. Similarly, somatostatin was proposed to suppress the oxidative PPP phase by reducing G6PD activity, affecting ribose synthesis, and inhibiting the carbon flux into PPP [84].

miR-1 and miR-122

miR-1 has been reported to work as a tumor suppressor gene by targeting G6PD transcripts and inhibiting tumor growth and metastasis [85]. miR-1 levels are reduced in many tumors as evidenced by the increased proliferation observed in high-risk papillomavirus-associated human cervical cancer cells [86]. In cardiovascular cells, miR-1 increased oxidative stress through binding to the single 3′-UTR complementary site of G6PD and superoxide dismutase transcripts [87]. Moreover, G6PD transcripts harbor 2 miR-122 binding sites in their 3′-UTR regions. In HepG2 hepatocellular carcinoma cells, the combination of miR-1 and miR-122 synergistically reduced G6PD expression and its enzymatic activity [88]. These results highlight the therapeutic use of miR-1 and miR-122 by inhibiting the PPP through suppressing G6PD.

6PGD Inhibitors

6PGD has been documented to be overexpressed in several cancers including colorectal [89], cervical intraepithelial [90], thyroid [91], and lung tumors [28]. 6PGD is stimulated by lysine acetylation [92]. Three potential therapeutic inhibitors of 6PGD are discussed below.

Physcion

Physcion, an active component of the medicinal plant Radix et Rhizoma Rhei, is an anthraquinone derivative, small-molecule that effectively inhibits 6PGD [91]. Purified physcion and its more soluble derivative S3 (1-hydroxy-8-methoxy-anthraquinone), inhibit purified human 6PGD at an IC_{50} of approximately 39 and 18 μM, respectively [92]. The molecular crystal structure of 6PGD suggests that physcion binds near to the 6-PG substrate site on 6PGD [92]. Physcion interacts hydrophobically with the residues Met15, Lys 76, Lys 261, and His 452 and forms a hydrogen bond with Asn 103 in this area of the enzyme.

Physcion was shown to inhibit cisplatin-resistant ovarian C13* cancer and lung adenocarcinoma A549DDP cancer cells proliferation. In ovarian OV2008 and C13* cancer cells, the decrease in cell proliferation was associated with a reduction in 6PGD activity. Similar results were observed in lung adenocarcinoma A549 and A549D-DP cells [92]. Physcion induced apoptosis in cervical cancer and lung carcinoma cells [92, 93]. The cytotoxic effect of physcion on cancer cells is well tolerated in preclinical studies. This drug showed minimal effect on the proliferation of human dermal fibroblasts and on immortalized human melanocytes. Physcion significantly decreased tumor volume when administered at 20 and 40 mg/kg/day in mice [94]. Moreover, the physcion pretreatment of ovarian and lung cancer cells reduced cisplatin resistance and revealed a synergistic effect of both drugs. Physcion also enhanced the activity of paclitaxel when administered in combination in xenograft models [93].

3-Phosphoglycerate

3-Phosphoglycerate (3-PG), an intermediate of glycolysis and the Calvin cycle, has been found to be a direct competitive inhibitor of 6PGD. Reports have shown that the attenuation of the glycolytic enzyme phosphoglycerate mutase 1, which normally regulates 3-PG levels, leads to an accumulation of 3-PG and subsequent inhibition of the oxidative PPP [95].

miR-206 and miR-613

Dysregulation of miRNA has been associated with chemotherapy resistance. For instance, miR-206 and miR-613 were found to be reduced in cisplatin-resistant cells [95]. Upon subsequent examination, the investigators found that these miRNAs are direct inhibitors of 6PGD gene expression. It is suggested that miR-206 and miR-613 have single binding domain sites on the 3′UTR of 6PGD. In combination, miR-206 and miR-613 reduced $NADPH/NADP^+$ ratio, increased glycolytic lactate flux, and ATP levels [96].

Nonoxidative Phase Inhibitors

In this section, we discussed the properties of a set of synthetic and natural nonoxidative PPP inhibitors, namely, inhibitors of TKT and TALDO that could be used to treat cancer and restore sensitivity to chemotherapy (Table 1).

TKT Inhibitors

TKT is a main enzyme of the nonoxidative PPP reported to be upregulated in several cancers. TKT is essential for cancer growth due to its effect on NADPH production and on carbon intermediates transfer for nucleotides synthesis and glycolysis reentering [97]. Three main inhibitors of TKT in clinical or preclinical setting are discussed below.

Oxythiamine

Oxythiamine (4-hydroxythiamine) is an irreversible noncompetitive inhibitor of the TKT enzyme [98]. Oxythiamine is pyrophosphorylated by thiamine pyrophosphokinase giving rise to oxythiamine pyrophosphate, which has structural similarity to thiamine pyrophosphate [99]. Thiamine is an essential cofactor of the TKT enzyme; thus, oxythiamine may serve as a thiamine antimetabolite analog of this key PPP enzyme. Although its mechanism of action remains to be elucidated [100], oxythiamine seems to mainly dock onto the active site of TKT by binding to Ser49, Lys84, Glu128, His160, and Lys218 residues, with Glu128 being the preferred inhibitory site [101]. In yeast infections, oxythiamine has been used to synergize with antifungal drugs [102]. Interestingly, oxythiamine was shown to significantly suppress tumor proliferation and increase G_0/G_1 cell cycle arrest in Ehrlich's ascites tumor mouse models in a dose-dependent manner [103]. Oxythiamine inhibitory effects were also shown to be related with a reduction in the activity of the MAPK pathway in the pancreatic Mia PaCa-2 cells [104]. Low and high doses of oxythiamine were documented in a subcutaneous xenograft cancer model where this drug was able to impede invasion and migration of Lewis lung carcinoma and to inhibit the activity of metalloproteinases-2 and 9 [105].

Oxythiamine has been reported to be used in combination with other drugs such as lovastatin and was shown to decrease TKT protein levels and to inhibit thyroid ARO cancer cell line proliferation [106]. Moreover, oxythiamine was shown to inhibit the carbon flux into the PPP, an effect enhanced when oxythiamine combined with somatostatin in Mia PaCa-2 cell line [84]. The combination treatment of 6-AN and oxythiamine increased DNA damage, $NADP^+/NADPH$ ratios, and ROS-induced apoptosis in thyroid cancer cell lines [62].

Genistein

Genistein is a natural soy plant-derived isoflavonoid with clinical and epidemiological significance that acts through a variety of mechanisms including antioxidant, estrogenic activities, and metabolic regulation [107–109]. It is successfully used as a tyrosine-kinase inhibitor to treat chemotherapeutic-resistant acute childhood, and chronic adulthood lymphoblastic leukemia [110]. Genistein significantly inhibited glycolysis of hepatocellular carcinoma cells by reducing the activity of hypoxia-inducible factor 1 alpha and inactivating hexokinase 2 and GLUT1 [111]. Boros et al. [112] reported that increasing dosage of genistein reduced Mia PaCa-2 cells ability to synthesize ribose for RNA synthesis. The mechanism of action is primarily through inhibiting the nonoxidative TKT reaction of the PPP by blocking nucleic acid synthesis. This was evident based on the mass isotope distribution analysis differential positioning of labeled carbon glucose isotopes tracing in pancreatic cancer cells upon genistein treatment [112]. In addition, genistein can prevent the proliferation of primary rhabdomyosarcoma, glioblastoma, embryonic carcinoma, and hepatocellular carcinoma cells, arrest cell cycle progression, and induce apoptosis [113]. It was also shown to reduce the adhesion and metastasis of prostate, lung, breast, and pancreas cancer cells by suppressing NF-κB, and protein kinase B transcription factors [114–116]. The combination of genistein with sorafenib was shown to improve the sensitivity of sorafenib-resistant hepatocellular carcinoma cell lines [111]. Several reports also indicate that genistein provides successful synergy when used in combination with tamoxifen in mammary tumors [117], with methotrexate in leukemia [118], and with cisplatin in ovarian cancer [119].

miR-497

miR-497 mainly functions as a tumor suppressor gene reduced in many types of cancer. Its alteration by transcriptional factors and genomic and epigenetic modifications affects the proliferation, angiogenesis, and apoptosis of cancer cells [120]. miR-497 has been recognized to be a negative regulator of cisplatin resistance in ovarian cancer [121] and cervical cancer [122]. The enhanced expression of miR-497 sensitizes HeLa cells to cisplatin treatment. Upon further investigation, miR-497 was found to be a direct inhibitor of its downstream target TKT enzyme (Yang et al. [122]). Similarly, treatment of HeLa and SiHa cervical cancer cells with miR-497 significantly downregulated both mRNA and protein expression levels of TKT. Mechanistically, these findings were explained by miR-497 inhibitory effect on TKT, causing a significant reduction in GSH levels and hence a compromised detoxifying ability. Notably, miR-497 has been used in conjunction with many chemotherapeutic drugs to enhance their effect on cancer cells, namely, in combination with 5-fluorouracil (5-FU) in colorectal cancer [123] and re-sensitized pancreatic cancer to gemcitabine and erlotinib [124].

TALDO Inhibitors

TALDO catalyzes the second reaction of the nonoxidative PPP driving the conversion of G3P and sedoheptulose-7-phosphate into F6P and erythrose-4-phosphate. TALDO is upregulated and implicated in cancer progression [125]. In *Caenorhabditis elegans*, TALDO inhibition reduced mitochondrial respiration, activated mitochondrial unfolded protein response, and induced longevity responses [126]. Similarly, mammalian mitochondrial function is also impacted when deficient for TALDO [127]. Patients with deficient TALDO showed reduced mitochondrial membrane potential, augmented mitochondrial mass, and elevated H_2O_2 levels in their isolated lymphoblasts [128]. Moreover, TALDO-deficient mice were infertile due to impaired mitochondria in spermatozoa [127].

Fructose 1,6-Bisphosphate

Fructose 1,6-bisphosphate is an intermediate in the glycolytic pathway that has been shown to inhibit the activity of TALDO. In *E. coli*, fructose 1,6-bisphosphate has been demonstrated to have 2 binding sites on TALDO; competing with F6P but not with erythrose-4-phosphate [129]. Moreover, this key enzyme of the nonoxidative PPP can be inhibited by different phosphorus compounds. For instance, arabinose 5-phosphate, an aldopentose version of the substrate F6P that lacks the 1-carbon and 1-hydroxyl atoms [130], has been implicated in suppressing cancer progression in murine colon cancer [131]. In addition, the monosaccharide D-tagatose 6-phosphate which has several applications as antidiabetic [132], and antioxidant medication [133] has been shown to irreversibly inhibit TALDO [134]. These compounds have strong similar stereochemistry with F6P but form Schiff bases with the active site lysine on TALDO and proceed to inhibit its activity [129].

Conclusion

Cancer cell metabolism is driven by extensive cellular proliferation. The PPP is upregulated in many tumors whereby its major enzymes may represent targets for novel anticancer regimen. Intracellular NADPH is mainly produced by the PPP and is required for redox homeostasis maintenance, which is needed to combat oxidative stress. In this review, we explored different regulators and exogenous inhibitors of the PPP in various cancer cells. The PPP enzymes are major players in several human diseases, with G6PD deficiency being the mostly reported metabolic disorder. However, G6PD, the rate-limiting PPP enzyme, plays a pro-survival role in cancer affecting cell proliferation and cell death. In diabetes, the nuclear factor E2-related factor 2, an oxidative stress regulated transcription factor, increased the expression of major PPP enzymes to promote cellular metabolism and contributed to cancer development [135]. PPP inhibitors, alone or in combination with conventional therapies, offer new treatment strategies especially in chemotherapy-resistant patients. For instance, cisplatin resistance has been linked to the PPP oxidative phase upregulation. Therefore, the inhibition of the PPP in combination with cisplatin-sensitized tumor cells to chemotherapy [45]. Furthermore, the combination treatment with PPP inhibitors and 5-FU-sensitized 5-FU-resistant colorectal cancer cells to chemotherapy (unpublished data). p53, the most frequently inactivated gene in cancers, blocks PPP through the inhibition of G6PD dimerization and activation [27]. Restoring p53 function is a promising strategy in cancer therapy that aims at inhibiting PPP and therefore cancer cell growth [136]. In summary, although many anticancer molecules targeting the PPP are being currently investigated, more research is required to identify novel oxidative and nonoxidative PPP inhibitors from natural or synthetic sources that can offer better efficiency and specificity and less toxicity. The surge of numerous studies demonstrating how cancer cells hijack the PPP to optimize their survival highlights the importance of integrating PPP inhibitors in cancer therapy.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

N.G., C.E.-B., and N.D. contributed to conception and design. N.G., C.E.-B., K.A., R.E.-K., and N.D. contributed to writing – original. N.G., C.E.-B., and N.D. contributed to draft preparation. N.G., C.E.-B., K.A., R.E.-K., J.U., and N.D. contributed to revision.

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