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Short review

G6PD: A hub for metabolic reprogramming and redox signaling in cancer

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ABSTRACT

Metabolic hubs play a major role in the initiation and development of cancer. Oncogenic signaling pathways drive metabolic reprogramming and alter redox homeostasis. G6PD has potential oncogenic activity and it plays a pivotal role in cell proliferation, survival and stress responses. Aberrant activation of G6PD via metabolic reprogramming alters NADPH levels, leading to an antioxidant or a pro-oxidant environment which can either enhance DNA oxidative damage and genomic instability or initiate oncogenic signaling. Nutrient deprivation can rewire metabolism, which leads to mutations that determine a cancer cell's fate. Deregulated G6PD status and oxidative stress form a vicious cycle, which paves the way for cancer progression. This review aims to update and focus the potential role of G6PD in metabolic reprogramming and redox signaling in cancer.

The redox role of G6PD

The study of glucose-6-phosphate dehydrogenase (G6PD) began in earnest following the discovery that certain anti-malarial drugs cause hemolysis in patients with G6PD deficiency [1]. G6PD is the first and rate-limiting enzyme of the oxidative branch of the pentose phosphate pathway (PPP). Traditionally, G6PD has been considered as an antioxidant enzyme with a major biochemical function in the anabolic metabolism of ribose 5-phosphate for nucleotide synthesis and the regeneration of the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH) for reductive lipid biosynthesis and the regeneration of glutathione (GSH) to detoxify reactive oxygen species (ROS). However, the prooxidant role of G6PD in generating ROS via NADPH oxidase (NOX) has also gained much attention. NOX generates ROS to exert its microbicidal action, also known as the cytotoxic effect, in phagocytic cells, whereas

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the NOX-derived ROS can serve as signaling molecules for promoting cellular activities in many non-phagocytic cells, also known as the cyto-regulatory effect [2].

G6PD-derived NADPH has a substantial impact on cellular oxidative and nitrosative stress/damage responses and on cellular growth and proliferation. However, how G6PD acts as a double-edged sword in modulating the cellular redox status which affects cellular, especially in altering cellular metabolism in cancer biology has not been extensively reviewed. The modulation of the redox status by G6PD during cancer development is the primary focus of this review.

The role of G6PD in cancer development and resistance to cancer therapies

G6PD can be considered as having oncogenic activity because it is required for growth and survival in both normal and transformed cells. Its function is essential in cell survival and embryonic development through redox sensitive mechanisms [3]. Lower than normal levels of G6PD activity predisposes cells to pre-mature senescence and cell death, while severe G6PD deficiency results in teratogenesis and embryonic lethality [4]. Aberrant activation of G6PD causes elevated ROS leading to uncontrolled cell growth and differentiation [5]. Changes in G6PD activity up-regulates anti-apoptotic factors and down-regulates cell cycle proteins in human melanoma mouse xeno-grafts [6]. Increased G6PD activity and the increased ratio of pentose monophosphate to hexose monophosphate have been found during the late G1 and S phase in human colon cancer cells [7]. Deregulation of long noncoding RNA (LncRNA) is linked to an impaired cell cycle, cell proliferation, and cancer. Reduced levels of the LncRNA growth arrest-specific transcript 5 (GAS5), a tumor suppressor, is associated with cancer aggressiveness [8]. Knockdown of GAS5 induces G1/S cell cycle progression through up-regulation of cyclin and Bcl-2 expression. Reduced GAS5 up-regulates G6PD and NOX4, resulting in an imbalanced redox environment in multiple myeloma cells [9]. The LncRNA protein disulfide isomerase family A member 3 pseudogene 1 (PDIA3P) regulates growth and chemotherapy resistance in multiple myeloma through interacting with c-Myc, a sequence-specific DNA-binding protein required for cell cycle progression. The interaction enhances PDIA3P transactivation. This results in its binding to the G6PD promoter, leading to an increase in G6PD activity and the PPP flux [10]. Phosphorylation of G6PD by a mitotic regulator polo-like kinase1 (Plk1) promotes G6PD dimer formation and coordinates PPP flux and cell cycle progression in cancer cell proliferation [11].

Table 1 Proteins regulating G6PD/PPP activity or flux.

Protein	Regulation	Reference
Transcription factor		
HIF	Up	[36]
Nrf-2	Up	[41]
Snail	Up	[70]
TAp73	Up	[53]
TP53	Down	[46]
Kinase		
ATM	Up	[56]
AKT	Up	[59]
c-Src	Up	[20]
PI3K	Up	[59]
PAK4	Up	[47]
PLK-1	Up	[11]
Cyclin D3-CDK6	Up	[33]
AMPK	Down	[64]
Others		
ID1	Up	[26]
mTORC1	Up	[66]
TGFβ1	Up	[29]
PDIA3P	Up	[10]
TIGAR	Up	[76]
PTEN	Down	[62]

The notion of G6PD having potential oncogenic activity is not unprecedented. Hyperactive G6PD activity has been found in many types of cancer cells and is linked to the characteristics of cancer cells, including transformation, metastasis and resistance to treatment [12]. G6PD up-regulation can serve as a surrogate marker for cancer staging and is an indicator of a poor prognosis [13]. Metabolic flux and labelling analysis reveals that nearly all pyruvate is produced from glycolysis and not the PPP in non-transformed breast cancer cells [14]. Increased PPP flux and doubled production of ribose are found in transformed and metastatic breast cancer cells compared to non-transformed cells. Consistent with the altered metabolic flux through the PPP, G6PD is a major contributor to invasion and migration in hepatocellular carcinoma [15]. G6PD is increased at the later but not the early stage of breast cancer brain metastasis as found by proteomics [16]. Transketolase of the non-oxidative branch of the PPP is considered as a hallmark of metastasis [17]. This contradiction suggests that differential metabolic flux may be determined by different progression stages in specific cancers.

That G6PD has potential oncogenic activity originates from the observation that G6PD is an angiogenic factor [18]. G6PD modulates endothelial cell growth, migration and capillary formation mediated by vascular endothelial growth factor (VEGF)-stimulated eNOS activity and nitric oxide generation [19]. Impaired vessel outgrowth from the thoracic aorta is found in G6PD-deficient mouse. The nonreceptor tyrosine kinase Src has many roles in cancer, including cell survival, proliferation, adhesion, angiogenesis, and migration. C-Src phosphorylates hexokinases HK1 and HK2, and promotes glycolysis leading to tumorigenesis and metastasis [20]. C-Src also directly phosphorylates G6PD and regulates VEGF-mediated endothelial cell responses [21].

G6PD activity may be critical for the response to radiotherapy and chemotherapy in cancer cells [22–24]. G6PD-derived endogenous reductants, such as NADPH and GSH, determine whether or not cancer cells are sensitive or resistant to apoptosis when stressed. Simultaneous use of inhibitors of glycolysis and G6PD, 2-deoxy-D-glucose (2-DG) and 6-aminonicotinamide (6-AN) respectively, enhances radiation damage selectively in malignant cells by a mechanism involving non-coordinated expression of antioxidant enzymes [23]. Accumulation of reactive oxygen species (ROS), reduced NADPH/$NADP^+$ and GSH/GSSG ratios have been observed in these cells 24 h after irradiation. Overexpression of the oncogene Inhibitor of differentiation-1 (ID1) is associated with a poor prognosis and plays a role in chemotherapy and

radiotherapy resistance [25]. Knockdown of Id1 reduces NADPH and G6PD activity and increases ROS. Reduction of ID1 also decreases cell proliferation and induces apoptosis in oxaliplatin-resistant hepatocellular carcinoma (HCC) cells [26].

G6PD can affect the efficacy of cancer drugs leading to drug resistance. Overexpression of G6PD and G6PD mRNA is a poor prognostic indicator in patients with colorectal cancer (CRC). G6PD knockdown reduces NADPH/$NADP^+$ and GSH/GSSG ratios as well as the H_2O_2 level in CRC cell lines [27]. G6PD suppression through RNAi against G6PD or NRF2 prevents oxaliplatin-induced apoptosis in CRC cells. G6PD knockdown also increases oxaliplatin sensitivity in both CRC cell line-based and patient-derived xenograft (PDX) models [27]. The production of lactate and other acidic metabolites due to increased G6PD and glycolysis causes an extracellular acidic microenvironment which favors cancer invasiveness by interrupting the action of weak base anti-cancer drugs [28]. G6PD expression is responsible for cisplatin resistance in non-small cell lung cancer (NSCLC) cells. Transforming growth factor beta 1 (TGFβ1) induces G6PD activity by activating transcription of the forkhead box protein M1-high mobility group AT-hook 1-G6PD (FOXM1-HMGA1-G6PD) pathway [29]. While exogenous TGFβ1 confers resistance to cisplatin, disruption of the TGFβ1-FOXM1-HMGA1-G6PD axis sensitizes NSCLC cells to the drug. Over expression of G6PD contributes to the development of multi-drug resistance (MDR) in cancer cells. Compared to doxorubicin-sensitive human colon cancer cells, doxorubicin-resistant cells have increased GSH, MDR-related proteins (MRPs) expression and doxorubicin clearance [30]. These findings indicate that G6PD participates in the metabolism or the detoxification of xenobiotics and anti-cancer drugs through a redox-regulated pathway [31].

Modulation of G6PD by oncogenic and metabolic regulators

The hallmark of cancer is the preference of glycolysis for glucose utilization rather than oxidative phosphorylation even in the presence of oxygen. This is known as aerobic glycolysis or the Warburg effect [32]. Cancer cells utilize a large amount of glucose compared to normal cells and convert it to lactate, which is excreted. The advantage to cancer cells lies in rapid production of ATP via glycolysis for cell proliferation and the accumulation of glycolytic intermediates for cell growth. This enables cancer cells with a capacity to outcompete normal cells even in adverse conditions. This unique feature may be related to the upstream regulation of G6PD by oncogenic and/or metabolic regulators.

Cyclins and cyclin-dependent kinases (CDks) are cell cycle components important for that affect cell proliferation and metabolism. Phosphofructokinase, platelet (PFKP), the main isoform of PFK-1, is phosphorylated and inactivated by cyclin D3-CDK6 [33]. PFKP suppression results in the movement of glycolytic intermediates towards the PPP and the serine pathway. Depletion of cyclin D3-CDK6 reduces NADPH and GSH, while increasing ROS in T-acute lymphoblastic leukemia (T-ALL) cells. Supplementation with NAC or a SOD mimetic scavenges ROS and protects T-ALL cells from apoptosis. These findings indicate that the metabolic reprogramming of the PPP is associated with cell survival and redox homeostasis.

Hypoxia-inducible factor (HIF) is an important metabolic regulator associated with G6PD [Table 1]. HIF, the central regulator of oxygen homeostasis, modulates angiogenesis by affecting endothelial cells, including cell survival and proliferation, cell invasion and glucose metabolism. The glycolytic end products, including pyruvate and lactate, stimulate the accumulation of HIF-1alpha [34]. Activation of G6PD by hypoxia is implicated in cancer cells and pulmonary remodeling [35,36]. Chronic exposure of hypoxia induced by cobalt chloride and dimethyloxalylglycine up-regulates G6PD gene expression in rat adrenal gland cells [37]. Increased G6PD and HIF-1 expression in glutamate-induced neural stem/progenitor cells in the rat mature retina suggests that PPP flux controls the fate of neural stem/progenitor cells [38].

Nuclear factor erythroid 2-related factor 2 (Nrf2), a basic leucine zipper (bZIP) transcription factor, which maintains cellular redox homeostasis and protects cells from oxidative stress, is another factor closely related to G6PD. The inactive form of Nrf2 is maintained in the cytosol by ubiquitination through Kelch-like ECH-associated protein 1 (Keap1) and Cullin 3. Oxidative stress disrupts the Keap1-Cul3 ubiquitination followed by the translocation of Nrf2 into the nucleus. Overexpression of Nrf2 has been found in cancer cells [39]. Suppression of Nrf2 and overexpression of Keap1 down-regulates the PPP enzymes, including G6PD and transketolase in metastatic breast cancer cells [40]. G6PD is required for Nrf2-dependent tumor proliferation mediated by the constitutive expression of Phosphoinositide 3-kinases (PI3Ks)-Akt. Overexpression of Nrf2 and knockdown of Keap1 enhance G6PD and HIF-1 expression in breast cancer cells. Mechanistically, Nrf-2 up-regulates Notch1 through the G6PD/HIF-1 pathway. Nrf2 activates antioxidant enzymes, up-regulates several oncogenes unrelated to antioxidant function, down-regulates lipid metabolic enzymes as well as interacting with microRNAs (miRNA) [41]. miR-1 and miR-206 suppress G6PD expression in cervical cancer cells by targeting the 3' UTR sequence [42,43]. Continuous activation of Nrf2 decreases miR-1 and miR-206 expression, leading to enhancement of G6PD activity and PPP flux [44].

The involvement of G6PD in cancer can be mediated by factors affecting the cell cycle, such as the tumor suppressor TP53 (p53). p53 is a transcription factor for inducing cell cycle arrest, apoptosis and maintaining genomic stability. It regulates cell survival and cell death through post-translational modification and intracellular redox status [45]. p53 is also the most frequently mutated gene in many cancers. p53 regulates the PPP by directly binding to G6PD, preventing its dimerization [46]. The p21-activated kinases 4 (PAK4) is up-regulated during cancer development, thereby supporting cancer cell proliferation. PAK4 binds to murine double minute 2 (Mdm2), an inhibitor of p53. PAK4 interacts with G6PD and enhances G6PD activity through promoting the degradation and ubiquitination of p53 in colon cancer cells [47]. It has been proposed that cancer-associated p53 mutations lift the restriction of G6PD and activate PFK-1, resulting in enhanced PPP flux and glycolysis, respectively [48]. The glycolytic enzyme phosphoglycerate mutase 1 (PGAM1) is frequently up-regulated in cancer cells lacking p53 [49]. PGAM1, catalyzing 3-

phosphoglycerate (3-PG) to 2-phosphoglycerate (2-PG), is required for cancer cell proliferation and tumor growth. Knockdown of PGAM1 inhibits PPP flux and leads to the accumulation of 3-PG, which suppress 6-phosphogluconate dehydrogenase (6PGD) but not G6PD [50]. In a comparative study using a bioprocessing culture, an inverse correlation of differential protein expression of G6PD and PGAM1 has been found in Chinese hamster ovary cells [51].

A structural homolog of p53, TAp73 is also an upstream regulator of G6PD. TAp73 plays a key role in the support of proliferation and promotion of the Warburg effect in cancer cells [52]. Unlike p53, there are rare mutations found in TAp73. TAp73 can transactivate p53-targeted genes, including G6PD. TAp73 deficiency induced-defective growth can be rescued by G6PD overexpression in human osteosarcoma epithelial cells, human lung cancer cells and mouse embryonic fibroblasts [53]. The inhibition of Ras-Tap73-G6PD signaling by Zoledronic acid, a therapeutic for bone disorders, suppresses G6PD activity and cell proliferation in bladder cancer cells [54]. These findings suggest a central role for G6PD in cancer cell proliferation and metabolism regulated by TAp73.

G6PD can participate in cancer development via Ataxia telangiectasia mutated (ATM) kinase which is required for regulating the cell cycle and for repairing double strand breaks (DSBs) [55]. Upon DNA damage, ATM phosphorylates Hsp27 and stimulates G6PD activity, promoting nucleotide synthesis for the repair of DSB [56]. Mutations of FMS-like tyrosine kinase 3 (FLT3) frequently trigger cell proliferation and survival in acute myeloid leukemia (AML) [57]. Failure of achieving long-term remission by FLT3 inhibitors in treating AML is ascribed to FLT3 mutation-derived resistance. Inactivation of ATM or its effector G6PD increases sensitivity to apoptosis induced by an FLT3 inhibitor [58].

Other oncoproteins linking G6PD with cancer include phosphoinositide 3-kinases (PI3Ks) which are involved in cellular transformation and cancer development. Mutations of the p110 alpha subunit of PI3K (PIK3CA) induces downstream AKT signaling and supports growth factor-independent proliferation. PI3K enhances glycolysis by upregulating expression of the glucose transporter and phosphofructokinase activity through the PI3K/AKT pathway. Insulin-induced G6PD expression is rapamycin-sensitive and is transcriptionally regulated by the PI3K/AKT pathway in hepatocytes [59]. G6PD status is also regulated by the AKT pathway in bladder cancer cells. G6PD knockdown enhances apoptosis, and reduces ROS accumulation and the phosphorylated AKT/AKT ratio [60]. The phosphatase and tensin homologue (PTEN), a p53-targeted tumor suppressor, negatively regulates PI3K. The mutation and loss-of-function of PTEN is implicated in heritable and sporadic cancers [61]. PTEN suppresses the PPP by interrupting pre-mRNA splicing of G6PD in liver cancer cells [62].

An additional cell cycle regulator associated with G6PD in cancer development is AMP-activated protein kinase (AMPK). AMPK affects cell growth and energy metabolism. AMPK senses intracellular ATP changes and restores ATP through phosphorylation of downstream targets, such as acetyl CoA carboxylase (ACC), 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMG-CoA), mTOR complex 1 (mTORC1) and p53 [63]. AMPK negatively regulates G6PD expression [64]. Upon metabolic stress, AMPK suppresses protein synthesis and cell proliferation by inhibiting mTOR, thereby preserving energy and cellular resources. Overexpression of G6PD is correlated with elevated mTORC1 activity, which in turn is correlated with a poor prognosis in acute myeloid leukemia [65]. mTORC1 enhances the expression of G6PD through the sterol regulatory element-binding protein (SREBP) in human embryonic kidney cells [66].

Involvement of G6PD in metabolic reprogramming upon stress and DNA damage

Cell survival depends on the adaptation to stress. Oxidative stress depletes the NADPH pool and alleviates the inhibition of G6PD leading to the activation of the PPP which is inhibited during normal growth through suppressing G6PD by NADPH [67]. Different metabolic requirements, such as ATP or NADPH or ribose, can switch on a distinct mode of metabolic flux [68]. Cancer cells need ribose more than ATP or NADPH for rapid growth in nutrient sufficient conditions but may need equal amounts of NADPH and ribose for proliferation. However, NADPH and ATP are required more than ribose in cancer cells under stress. Solid tumors detached from the extracellular matrix activate apoptotic pathways. Matrix detachment causes depletion of ATP and glucose as well as increased oxidative stress. To survive, cancer cells rewire metabolic flux to produce additional ATP and NADPH for meeting their energy needs as well as for balancing oxidative stress, respectively. Matrix detachment enhances G6PD expression [69]. Suppression of G6PD by siRNA knockdown or chemical inhibitors (DHEA, 6-AN) decreases glucose uptake and ATP and increases oxidative stress in detached breast cancer cells. The rescue of detachment-induced phenotypes by oncogene ErbB2 expression requires G6PD through the activation of PI3K and stabilization of the EGFR. Matrix detachment-induced energy reprogramming in breast cancer cells can also be reversed by the antioxidant N-acetyl-L-cysteine (NAC), a GSH precursor, or activation of AMPK [64]. Snail (SNAI1), a transcriptional repressor, regulates the epithelial–mesenchymal transition (EMT) in cancer cells. Knockdown of SNAI1 sensitizes cancer cells in a way that leads to their demise under metabolic stress, such as glucose deprivation [70]. SNAI1 inhibits glycolysis and redirects glucose to the PPP by suppression of PFKP in breast cancer cells.

Upon nutritional and genotoxic stress, cancer cells rewire metabolism from glycolysis to the PPP to obtain a sufficient supply of reductants such as NADPH to detoxify ROS. G6PD is activated rapidly for maximizing NADPH production in skin fibroblasts and keratinocytes during short-term oxidant and UV exposure [71]. Knockdown of G6PD renders sensitivity to oxidant-induced cell death in liver cancer cells [72]. Regeneration of GSH is impaired in G6PD-deficient liver cancer cells, and is worsened by treatment with the oxidant, diamide [73]. Upon diamide treatment, several metabolic pathways, including energy and amino acid metabolism, are affected. Diamide-enhanced NAD kinase activity is a compensatory action leading to an accumulation of NADPH in G6PD-deficient liver cancer cells [74]. NAC rescues diamide-induced cell death and GSH depletion in G6PD-deficient cells, suggesting that

G6PD is required for cell survival by maintaining an intracellular reductant environment and energy metabolism.

Beyond the contribution of genetics such as the buildup of multiple mutations in cancer, this disease has recently been considered as a metabolic disease shaped by the network between tumor cells and their surrounding environment. Metabolic reprogramming in cancer cells can be attributed to genotoxic insult-derived DNA damage, nutrient insufficiency, and impaired DNA repair. A network of DNA damage response (DDR) pathways has been established for maintaining genomic integrity. These include DNA repair, damage tolerance and cell-cycle checkpoint pathways [75]. DDR is involved in driving metabolic reprogramming regulated by ATM and ataxia telangiectasia and Rad3-related (ATR) kinases. ATM induces G6PD to generate NADPH and ribose in order to counteract the genotoxic stress [56]. p53 regulates the cell cycle, DNA repair and apoptosis by transactivation of downstream DDR genes at the promoter region. Induction of TP53-inducible glycolysis and apoptosis regulator (TIGAR) by p53 suppresses glycolysis and redirects glucose to the PPP [76]. In contrast to the traditional view that oncogenic mutations reprogram cancer cell metabolism, the unique microenvironment derived from rewired metabolism may lead to a rise of mutations. The availability of essential nutrients affects the fate of cancer cells by directly regulating mutations that control their survival or demise. Folate deficiency causes chromosome breaks by incorporating excessive uracil into DNA. It increases the risk of colorectal cancer [77]. Glucose depletion leads to mutations in the KRAS pathway in colorectal cancer cells [78].

DNA damage and repair pathways are critical in cancer development and cancer cell therapy [79]. Dysregulation of these pathways not only enhances genomic instability and the mutation rate, but also increases cancer heterogeneity [80,81]. This could result in the regulation of the DNA repair pathway by adding substrates from metabolic intermediates to nucleic acids and chromatin [82]. PPP-derived ribose is the main precursor for the synthesis of purines and pyrimidines. Genetic insult and hypoxia-induced DNA damage mediated by TIGAR can be reversed by supplementing human liver cancer cells with ribose [83].

Amino acid and metabolite levels determine the availability of intracellular nucleotides and influence the DNA repair pathway. Glutamine is essential for producing the intermediates inosine monophosphate and uridine monophosphate for purine and pyrimidine synthesis, respectively [84]. Deoxyribonucleotide triphosphate (dNTP) synthesis is dependent on the consumption of glucose and glutamine. Knockdown of ATM increases glucose and glutamine consumption, which is a characteristic of cancer cell metabolism. Nucleotide depletion-induced replication stress is important in cancer cell initiation. Cancer cells inactivate ATM in response replication stress by rewiring cellular metabolism to the PPP through p53-mediated G6PD up-regulation [85]. ROS is implicated in the relationship between metabolism and the DNA repair pathways. Increased ROS causes DNA oxidative damage by inducing single strand breaks. These lesions interrupt DNA replication and doubles DNA strand breaks [86]. Intracellular ROS-scavenging molecules and enzymes are required for counteracting DNA damage caused by ROS. G6PD-derived NADPH is the main source for regenerating GSH, which is synthesized from cysteine, glycine and glutamate. Decreased levels of glutamate due to diminished glutamate dehydrogenase (GDH-1) activity, which relies on NADPH, is associated with impaired NADPH generating enzymes, including G6PD and IDH1 [87]. GSH peroxidase detoxifies peroxide compounds and oxidizes GSH. The regeneration to the reduced form of GSH is catalyzed by NADPH-dependent GSH reductase. Another source of NADPH comes from one-carbon metabolism, which includes the serine synthesis pathway and the glycine cleavage system (GCS). Cancer cells alter these pathways to maintain one carbon donors for cellular proliferation [88]. Serine hydroxymethyltransferases (SHMTs) convert serine to glycine and generate methylene-THF. Methylene tetrahydrofolate dehydrogenases (MTHFDs) utilize NADP as a substrate to produce NADPH. Like G6PD, several enzymes of the serine synthesis pathway are directly regulated by Nrf2, including activating transcription factor 4 (ATF4), phosphoglycerate dehydrogenase (PHGDH), and phosphoserine aminotransferase 1 (PSAT1) [89].

Summary

Deregulated metabolism has long been considered as secondary to genomic abnormalities in cancer development. New evidence indicates that genetic alterations reprogram metabolic pathways by activating oncogenes or dampening tumor suppressor genes. G6PD, the core enzyme of the PPP, is closely linked to the development of cancer. Activated G6PD is exploited by cancer cells as a powerful weapon for proliferation and survival in an unfavorable environment. Ribose, NADPH and GSH, products of G6PD, are strategically utilized by cancer cells during growth, invasion, and metastasis as well as resistance to therapy. These measures enable cancer cells to tackle the cause of stress, which include oxygen deprivation, nutrient deficiency, ROS, RNS and DNA injury. Therapeutically, targeting G6PD in cancer cells is of great interest. However, the lack of a specific inhibitor hinders therapeutic development. A comprehensive understanding of the role of G6PD in the metabolism and in the redox regulation of tumorigenesis and cancer progression will provide a basis for establishing an additional and novel approach in the treatment of cancer.

Conflicts of interest

The authors declare no conflict of interest.

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