Journal of Vasyl Stefanyk Precarpathian National University
http://jpnu.pu.if.ua
Vol. 2, No. 1 (2015), 25-37

UDC 577.151.63+577.152.16+577.125.36+577.218+577.334
doi: 10.15330/jpnu.2.1.25-37

UNDERINVESTIGATED ROLES OF GLUCOSE-6-PHOSPHATE DEHYDROGENASE

DMYTRO GOSPODARYOV

Abstract. The review examines certain aspects of the reaction catalyzed by glucose-6-phosphate dehydrogenase (G6PDH) in living organisms of different taxa, from bacteria to humans. Particular emphasis is put to the role of G6PDH in iron homeostasis and lipogenesis. Prooxidant and antioxidant roles of G6PDH are also highlighted along with several currently known mechanisms of G6PDH regulation.

Keywords: NADPH, superoxide, thiol, iron-sulfur cluster, glutathione.

1. INTRODUCTION

Glucose-6-phosphate dehydrogenase (G6PDH) is an ancient enzyme, which is present in both, prokaryotes and eukaryotes. This dehydrogenase is the very first and regulatory step of pentose phosphate pathway (PPP). In turn, PPP interplays with many other important metabolic pathways in cells (Fig. 1). Indeed, PPP allows producing of ribose-5-phosphate, carbohydrate part of ribonucleotides as well as the metabolite of Calvin cycle in photosynthetic organisms. One of the products of the reaction catalyzed by G6PDH is reduced nicotinamide dinucleotide phosphate (NADPH). This compound is an essential reductant used in numerous biosynthetic processes [48]. Particularly, NADPH takes part in fatty acid and sterol synthesis, reduction of low and high molecular mass thiols [48], and consequently, in synthesis of heme and assembly iron-sulfur (Fe/S) clusters [14, 68]. These roles for NADPH, which is reduced mainly by G6PDH, characterize the latter as lipogenic and related to antioxidant defense enzyme. They underlie also specific regulation of G6PDH. It is known that the expression of the gene coding for G6PDH in multicellular organisms is regulated by transcriptional factors which are responsible for lipogenesis and antioxidant defense [3, 8, 42]. However, the lipogenic role of G6PDH is more pronounced in multicellular organisms which have lipid storages and insulin signaling. Indeed, NADPH does not react with either hydrogen peroxide or superoxide anion-radical directly, but instead reduces thiol-containing antioxidant proteins such as glutaredoxins and thioredoxins, and also tripeptide glutathione. Interestingly, all these antioxidant thiols are common for bacteria and humans. Using of NADPH as main thiol reductant adds a new layer of complexity in understanding of G6PDH role. Thus, glutaredoxins and thioredoxins, in addition to their antioxidant function, play also many metabolic roles. For instance, thioredoxin is used for the synthesis of deoxyribonucleotides from ribonucleotides [62]. This step integrates production of ribose-

5-phosphate in PPP and ribonucleotide biosynthesis with production of NADPH in PPP and deoxyribonucleotide biosynthesis. Reduced glutaredoxins are necessary for the assembly of Fe/S clusters and heme synthesis [14, 68] as it was mentioned above for NADPH. These roles of NADPH and reduced thiol-containing compounds may also partially explain development of hemolytic anemia in response to certain drugs for people with G6PDH deficiency that will be examined in more details in the review. The complexity and intertwining relationships between all processes which are related to G6PDH combined with huge amount of new data, demands scrupulous systematization. Despite the constant focus on G6PDH as an important enzyme, majority of past and recent reviews are devoted predominantly to G6PDH deficiency.

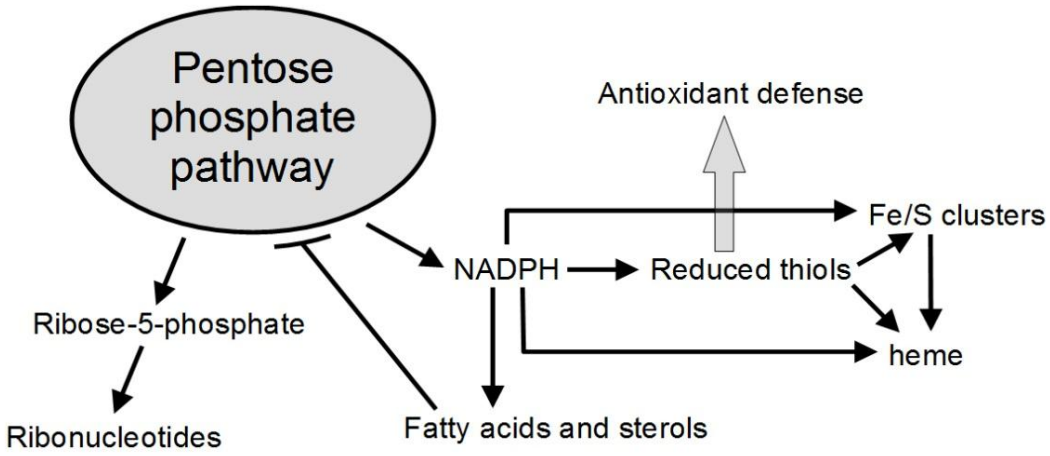

Fig. 1. Roles of pentose phosphate pathway in cells.

Thus, the goal of this review is to summarize and systematize the current knowledge on the roles of G6PDH in living organisms, from bacteria to humans. Particular emphasis is put on the points which were not emphasized previously, namely the role of G6PDH in Fe/S cluster biogenesis and the complex regulation of G6PDH activity, including responses to different environmental stimuli. This systematization is also required for better understanding of the integrated metabolic scheme for cells, tissues, organs and a whole organism. The crucial point here is that certain enzymes and metabolites of the organism can be set for distinct and specific roles. Particularly, despite so many important roles for G6PDH in cells, its deficiency is rarely characterized by a strong phenotype. The deficiency is exhibited as severe hemolytic anemia in response to redox-cycling compounds and may be accompanied by chronic granulomatous disease. However, there were no reports about disorders in lipid and sterol synthesis or nucleotide synthesis. The other example of such specific phenotype is fumarase deficiency which leads to predominantly renal cancer or leiomyomas [1], although fumarase is present in every cell and is an important enzyme in tricarboxylic acid cycle. The tissue-specificity of these and other similar diseases is poorly understood, and requires more profound understanding of metabolic integration, including signaling pathways which can be modulated by intermediates of key metabolic pathways.

2. G6PDH IN IRON-SULFUR CLUSTER HOMEOSTASIS

The gene *zwf* coding for G6PDH in enterobacteria is a member of the SoxRS regulon which coordinates defense systems against deleterious effects of superoxide anion-radical and hydrogen peroxide. Genes *sodA*, *acnA*, *fpr*, *fldA*, *fur*, *yggX*, and others which code for manganese-containing superoxide dismutase, oxidant-resistant aconitase, NADPH-ferredoxin oxidoreductase, flavodoxin A, ferric iron uptake regulator and putative Fe^{2+} transporter, respectively, are other members of this

regulon [21]. Superoxide dismutase (SOD) is the main enzyme detoxifying superoxide. This enzyme dismutates two molecules of superoxide yielding hydrogen peroxide and molecular oxygen. Importantly, superoxide is a very short living reactive oxygen species [21]. Thus, under intensive intracellular generation of superoxide or during attack of immune cells, catalase and peroxidases are a second line of the defense after SOD. Among peroxidases, glutathione peroxidase is one of the key enzymes for detoxification of hydrogen peroxide [65]. This enzyme uses tripeptide glutathione to reduce hydrogen peroxide as well as many other peroxides. Afterwards, the pool of reduced glutathione is replenished by *de novo* synthesis or in reaction catalyzed by glutathione reductase (GR) where NADPH is used as a reductant. This is a simple explanation of the regulation of *zwf* expression by superoxide. However, it is known that the gene coding for GR in *Escherichia coli*, *gorA*, is regulated by the OxyR transcriptional factor responding to hydrogen peroxide [40]. In contrast, G6PDH has so called "soxbox" and is regulated by the SoxS regulatory protein responding to superoxide anion-radical [11, 79]. Hydrogen peroxide may activate also SoxS target genes but there was no *zwf* among them [43, 81]. However, the increase in expression at the level of G6PDH activity in response to hydrogen peroxide treatment was described in other papers [60, 61]. Redox-cycling compounds may also drive OxyR-regulated genes [15]. Nevertheless, differential regulation of G6PDH and GR in *E. coli* suggests more specific role of G6PDH in response to superoxide attack. This specific role of G6PDH may supposedly be connected with repair of Fe/S clusters, the one of the main targets for superoxide. It is known that biogenesis of Fe/S clusters in bacteria and eukaryotes requires NADPH [12, 21, 49, 68] and is mediated by NADPH-dependent enzymes such as NADPH-ferredoxin oxidoreductase [12]. Remarkably, the latter enzyme is also under SoxS regulation [12, 21]. In addition, it was demonstrated that expression of SoxS targets can be triggered by changes of NADPH/$NADP^+$ ratio [26]. This demonstrates specific role for G6PDH in Fe/S cluster repair shared by bacteria and budding yeast *Saccharomyces cerevisiae*. Particularly, yeast strains deficient in G6PDH are auxotrophic for lysine and methionine. Metabolism of both these amino acids includes enzymes with Fe/S clusters and stages which require NADPH. Particularly, biosynthesis of lysine in yeast goes through the conversion of homocitrate to homoisocitrate [35]. This conversion is catalyzed by homoaconitase Lys4p, the enzyme containing Fe/S cluster and sensitive to superoxide treatment [34]. Additionally, lysine biosynthesis pathway includes two NADPH-consuming reactions, catalyzed by Lys2p and Lys5p, α-aminoadipate reductase and saccharopine reductase, respectively. Yeast methionine biosynthesis includes sulfite reductase Met5p, which also contains Fe/S clusters [72]. Sulfite reduction is simultaneously a NADPH-consuming step [66, 72]. In turn, the step catalyzed by phosphoadenylyl sulphate reductase requires thioredoxin as a reductant [72]. Thioredoxin is subsequently reduced by thioredoxin reductase, thus the thioredoxin reduction is also a NADPH-dependent step. Details of this regulation are shown on the scheme below (Fig. 2).

In humans, G6PDH deficiency causes severe erythrocyte hemolysis only after consumption of redox-cycling compounds contained in formulations of certain drugs and in foods like fava beans [6]. It means that despite importance for the whole organism, G6PDH is dispensable enzyme and its reduced activity does not result in strong phenotypes [6, 36]. It is believed that erythrocyte hemolysis under G6PDH deficiency is rather caused by superoxide and hydrogen peroxide than induced by redox-cycling agents directly [50, 78]. Thus, incapability of G6PDH-deficient cells to cope with superoxide toxicity results from glutathione depletion under NADPH deficit. Subsequently, superoxide and its derivatives, hydroperoxyl radical, hydrogen peroxide, and peroxinitrite oxidize many functional molecules in the cell, leading to its death. However, erythrocyte hemolysis may have also other causes, including those that anticipate the role of G6PDH in iron-sulfur cluster assembly. Particularly, ferrochelatase which catalyzes the final step of heme synthesis is a Fe/S-containing enzyme can be one of the potential candidates. Heme synthesis requires also involvement of other Fe/S-containing proteins such as ferredoxins [63]. Also, heme biosynthesis is a NADPH-consuming process [31]. Opposing to this concept, would be the fact that GR deficiency is characterized by similar symptoms that G6PDH deficiency [24]. However, it was recently found that glutathione plays an important role in Fe/S cluster biogenesis [27, 38].

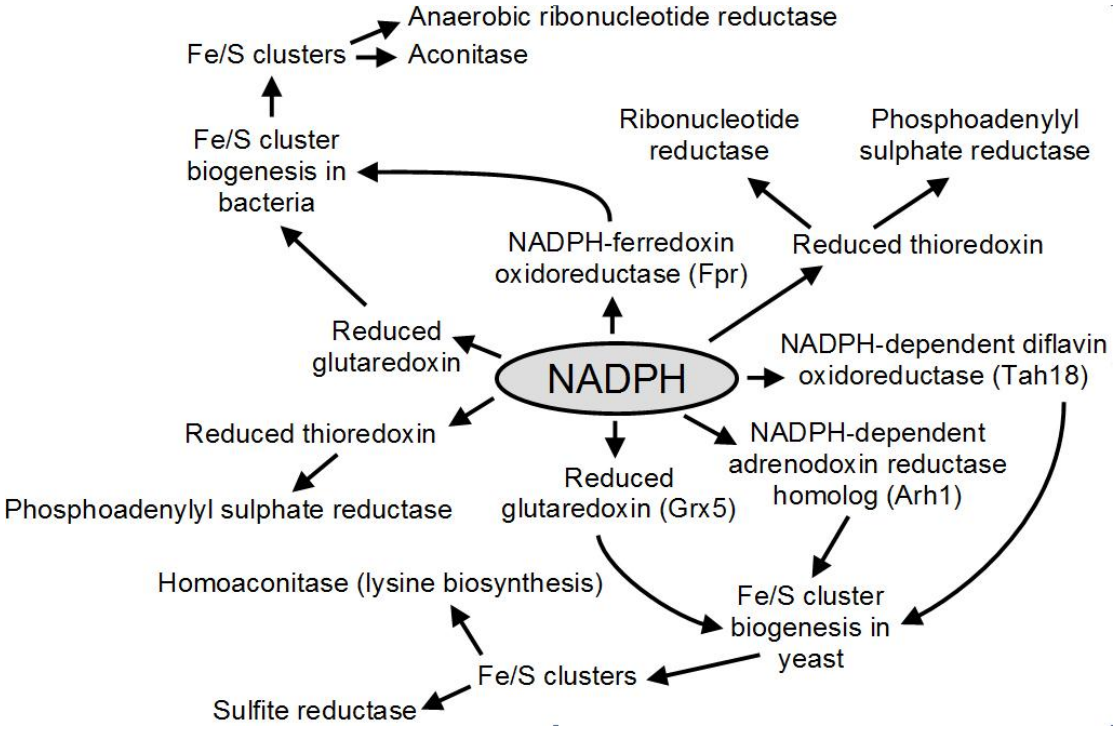

Fig. 2. Roles of NADPH in iron-sulfur cluster biogenesis.

Other reasons for hemolytic anemia at G6PDH deficiency can be related to involvement of NADPH in protection of erythrocyte membranes, particularly unsaturated fatty acids, against free radical attack resulting in lipid peroxidation, and/or its involvement in maintaining of correct redox state of Fe^{2+} in hemoglobin.

3. Antioxidant and Prooxidant Roles of G6PDH

As it was mentioned above, G6PDH is considered to be an enzyme closely related to antioxidant defense. The connection of G6PDH with antioxidant system is via NADPH which is further used for thiol reduction. However, it was highlighted above that thiols may equally be important for both, antioxidant defense and Fe/S repair. Thus, it is still difficult to distinguish between the antioxidant roles of G6PDH in either detoxification of peroxides, including hydrogen peroxide, by glutathione- or thioredoxin peroxidases, or in repair of cellular damage caused by reactive oxygen species (ROS). Indeed, impairment of Fe/S clusters may operate as prooxidants. Particularly, certain antioxidant enzymes, like catalase, contain heme and tightly bound NADPH (Fig. 3). As it was shown above, Fe/S-containing proteins, ferrochelatase and ferredoxins, are required for heme biosynthesis. Numerous Fe/S-containing proteins are involved in cellular energy metabolism. These proteins are in complexes I (NADH-ubiquinone oxidoreductase), II (succinate dehydrogenase), and III (ubiquinol-cytochrome c oxidoreductase) of mitochondrial respiratory chain as well as cytosolic and mitochondrial aconitases. Inhibition of mitochondrial respiratory complexes and aconitase may lead to increased intracellular ROS production by the respiratory chain. For instance, this increase in ROS production is obsered in case of mutations in gene *BCS1L*. This gene encodes an AAA family ATP-ase which is responsible for insertion of Rieske Fe/S center into the complex III [47]. Production of ROS can also be enhanced via disturbances in iron homeostasis since iron is a reactant in Fenton reaction, in which hydroxyl radical is formed from hydrogen peroxide [14, 39]. Interestingly, Fe/S clusters of the complex I themselves are

sites of ROS production [44]. Inhibition of aconitase may also prevent ROS-induced damage to a certain extent via blocking of citrate conversion and citrate accumulation. Citrate is itself an iron chelator and may show antioxidant properties [53], although citrate-iron complexes rather promote than hinder oxidative damage in many cases [73]. The complexity of the situation may be even higher if to take into account that NADPH is also used for the transport of iron and copper [20, 80], metals that present in active centers of antioxidant enzymes, catalase and SOD, respectively. The transport of these metals includes subsequent steps of reduction, oxidation, and permeation. The reduction step is mediated by NADPH-dependent enzymes ferric and copper reductases (Steap1-4 proteins in humans and Fre1-8p in budding yeast) [20, 80].

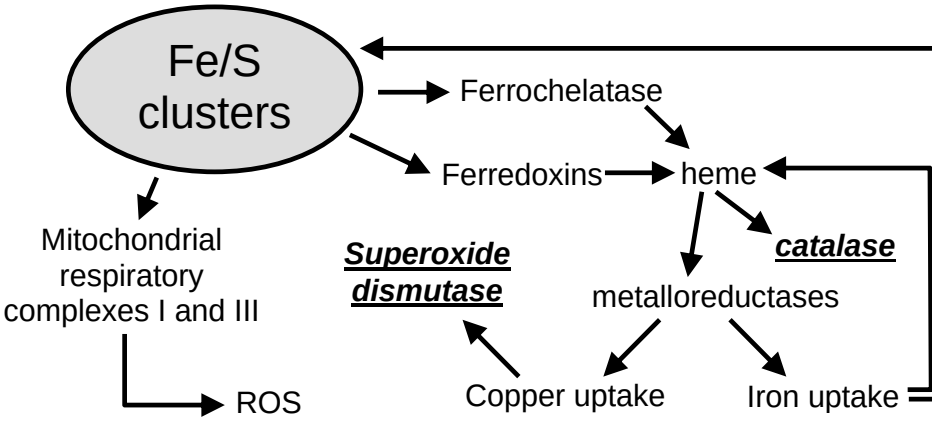

Fig. 3. Significance of iron-sulfur clusters for antioxidant defense. Antioxidant enzymes are underlined.

On the other hand, G6PDH may have also prooxidant role. In multicellular eukaryotes, NADPH is also used for superoxide production by NADPH oxidases [18]. Superoxide and its derivatives, including peroxynitrite, are used by immune cells to kill bacteria or eukaryotic parasites. Thus, G6PDH is an important enzyme for immune defense. Moreover, severe G6PDH deficiency was found to be accompanied by chronic granulomatous disease [2]. In some cases, deficiency of G6PDH and related decrease in superoxide production may confer certain advantages. For instance, apolipoprotein E-deficient mice with simultaneous lack of G6PDH showed less atherosclerotic lesions of aorta under high-fat feeding [45]. Interestingly, up-regulation of G6PDH accompanies cell proliferation, and consequently tumor formation [74]. Therefore, G6PDH activity should be strictly regulated in multicellular organisms.

4. Regulation of G6PDH Activity

The activity of G6PDH is mainly regulated at transcription level. Upstream region of the gene *zwf* that codes G6PDH in *E. coli* contains "soxbox", or SoxS-binding sequence AATCGACGGGTGGATAAGCGTT serving for regulation of *zwf* expression by superoxide via SoxRS system [79]. It is also known that G6PDH is regulated by the MarA transcription factor, which is responsible for bacterial resistance to multiple antibiotics [22]. In unicellular *S. cerevisiae*, expression of the *ZWF1* gene coding for G6PDH is shown to be regulated by the Yap1p transcription factor [32, 58]. It was also shown that G6PDH can be involved in high sugar stress tolerance by unknown mechanism [10]. In multicellular eukaryotes, expression of the gene coding for G6PDH is likely regulated in multiple ways because G6PDH is responsible for antioxidant defense and lipogenesis. The model of G6PDH regulation at the level of gene expression was proposed by Kletzien and colleagues [25]. It takes into account promoter regions via which the G6PDH expression can be controlled by insulin, polyunsaturated fatty acids, monasaccharides and glycerol. The analysis

performed by these authors revealed tissue-specific mode of G6PDH regulation by insulin and glucocorticoids, and epidermal growth factor via AP-1 (activator protein 1, heterodimer of protooncogens c-Jun and c-Fos) sites. The promoter of human G6PDH gene contains E-box (for binding regulatory proteins with basic helix-loop-helix motif), sterol regulatory element (SRE), and SRE-like sequence [3]. Additionally, Sp1 site was also found in the promoter of human gene encoding G6PDH [55]. The expression of G6PDH was found to be strongly up-regulated by sterol regulatory element binding protein 1a (SREBP-1a) and to the lesser extent – by SREBP-1c and SREBP-2 [3, 4]. The presence of E-box implies also regulation by carbohydrate response element binding protein (ChREBP). In turn, SREBPs and ChREBP are themselves activated via insulin signaling pathway [8]. Moreover, G6PDH demonstrated high activity in cancer cells due to upregulation via phosphatidylinositol-3-kinase (PI3K) along with other pro-oncogenic signaling proteins such as mTORC1 (mammalian target-of-rapamycin complex 1), K-ras (small GTPase), ATM (ataxia-telangiectasia mutated kinase), and protein kinase A. At the same time, anti-tumor proteins, transcription factor p53, protein phosphatase PTEN (phosphatase and tensin homolog), AMP-dependent protein kinase, and second messenger molecules, like cyclic AMP, regulate G6PDH activity negatively [23, 67]. Oxidative stress may induce G6PDH at transcriptional level via nuclear factor-erythroid 2-related factor-2 (Nrf2) [23, 67]. Indeed, antioxidant responsive element (ARE), the sequence ATGACACAGCA, was detected in the promoter of G6PDH gene [46]. This regulation has several more interesting links related to the noted above regulatory pathways. Particularly, Nrf2 is recognized as potentially pro-oncogenic regulatory protein [46, 64]. The activity of this transcription factor was revealed to be modulated by pro-oncogenic proteins like PI3K and downstream kinase Akt (protein kinase B) [46, 64]. On the other hand, Nrf2 could be involved in regulation of metal homeostasis as it binds to AREs of genes coding for ferritin L and metallothionein-1 as well as number of genes encoding antioxidant enzymes [7, 77].

Polyunsaturated fatty acids, such as arachidonic acid, can affect expression of G6PDH at posttranscriptional level via complex mechanism related to pre-mRNA splicing [55]. Arachidonic acid acted by multiple ways preventing induction of G6PDH expression by insulin and high carbohydrate diet. Particularly, arachidonic acid blocks insulin pathway by inhibition of PI3K, while activates kinase p38 [71]. Further, this polyunsaturated fatty acid was shown to decrease phosphorylation of serine-arginine-rich proteins, specifically SRSF3, which regulate pre-mRNA splicing by binding to exonic splicing enchancer sites [75]. At the same time, insulin increased phosphorylation of SRSF3 and resulted in correct splicing of G6PDH mRNA. Human gene coding for G6PDH consists of 13 exons. In case of incorrect splicing due to inhibition of SRSF3 binding, introns flanking the exon 12 are retained [75]. This posttranscriptional regulation comprises also splicing silencers, particularly, heterogeneous nuclear ribonucleoproteins (hnRNPs) K, L and A2/B1 which bind to the regulatory sites in G6PDH pre-mRNA near exon 12 in the starved state and dissociate during refeeding [17]. Recently, this mechanism was specified, and protein phoshatase PTEN, an anti-tumor protein which negatively regulates insulin signaling, was introduced to the scheme [19]. Protein phosphatase PTEN was shown to interact with hnRNP K, activating it, thus impeding correct splicing and lowering G6PDH activity. Simultaneously, PTEN activates glycogen synthase kinase 3β (GSK-3β) by dephosphorylation. This kinase phosphorylates, in turn, the co-activator of Akt kinase, the Tcl1 protein. This protein, known as an inducer of insulin signaling, interacts with hnRNP K, but inhibiting it, hence increasing G6PDH expression. The details of this regulation are shown on the figure Fig. 4. Such complex mechanism underlies hepatocancerogenesis [19] caused by disorders of insulin signaling pathway, and is also important in healthy tissue for relatively rapid response to refeeding after starvation [4].

There are many ways of G6PDH activity regulation at posttranslational level. It was found that G6PDH was allosterically regulated by NADPH/$NADP^+$ ratio [56, 67] and sterols [59, 67]. In cold-blooded animals, G6PDH was shown to be reversibly phosphorylated/dephosphorylated [70]. These posttranslational changes to G6PDH were observed in anoxia-tolerant animals like marine mollusk *Littorina littorea* and crayfish *Orconectes virilis* [29, 30], and animals with hypometabolic stages [9, 54]. In these animals, G6PDH is phosphorylated mainly by protein kinase G, and additionally by protein kinases A, calmodulin-dependent and AMP-activated protein kinases [9, 29, 30, 54]. The enzyme is

dephosphorylated by protein phosphatases 1 and 2C [29]. Here, G6PDH is likely a part of adaptive mechanism for prevention of oxidative damage caused by re-oxygenation after prolonged anoxia. Phosphorylated G6PDH was shown to be more active in comparison with dephosphorylated one. During anoxia and aestivation, G6PDH is phosphorylated, what results in changes in substrate affinities [9, 29, 30, 54] and enzyme activation.

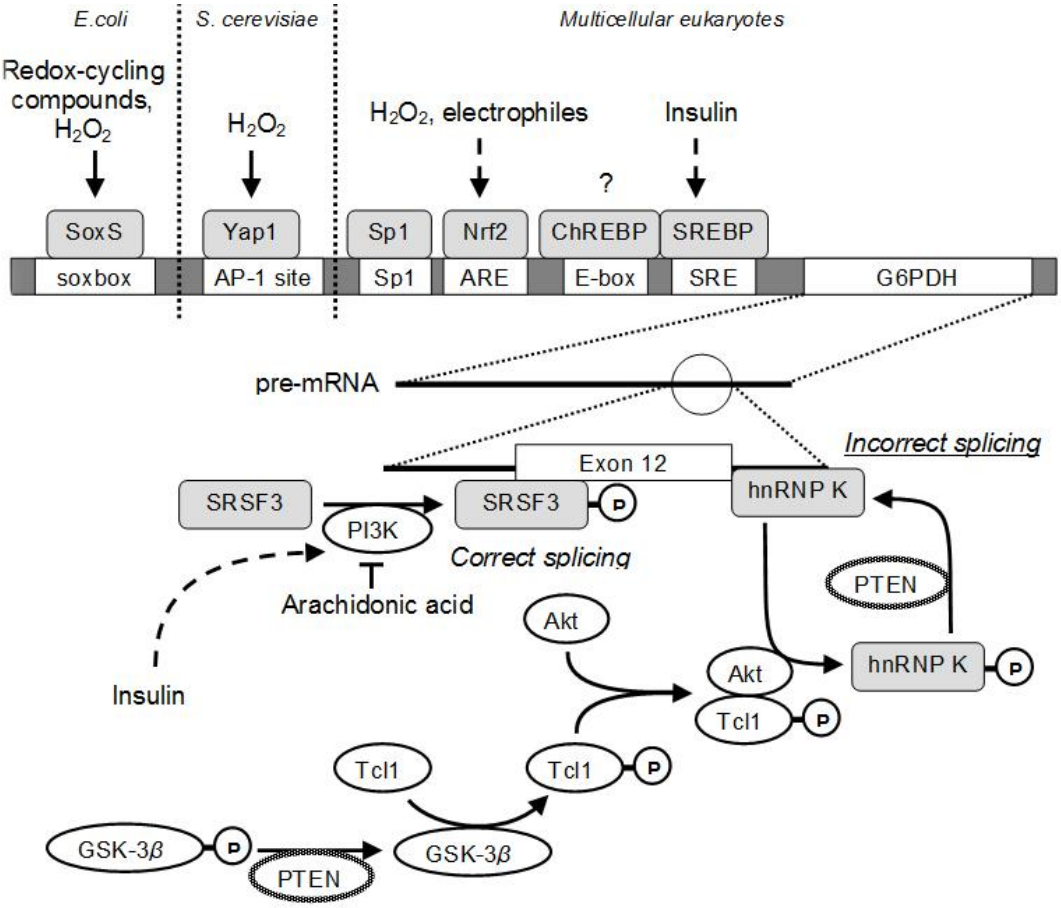

Fig. 4. Scheme of G6PDH expression regulation at transcription and posttranscription levels.

Strong oxidative stress may lead to irreversible oxidation of G6PDH resulted in its inactivation. For instance, G6PDH was inactivated during growth of catalase-deficient yeast on ethanol, a non-fermentable carbon source [41]. It was shown in this and other cases that G6PDH activity positively correlated with catalase activity, suggesting potential G6PDH protection against oxidation by catalase [5, 37]. However, there could also be other explanation for the link between G6PDH and catalase. Particularly, G6PDH and catalase activities also positively correlated in *Drosophila melanogaster*, although in this instance organism was not subjected to a strong oxidative stress [37]. Thus, activities of both enzymes are higher in fruit fly males as compared with females, and they both are higher on high carbohydrate diets as compared with low carbohydrate ones [37]. Both enzymes are involved in metabolism of fatty acids: catalase operates in peroxisomes during breakdown of very-long-chain fatty acids to decompose H_2O_2 produced as side product, while the reaction catalyzed by G6PDH produces NADPH for fatty acid biosynthesis and reduction of oxidized glutathione. At the same time, G6PDH is inhibited by certain fatty acids (e.g., arachidonic acid) at posttranscriptional level [55]. Low carbohydrate diet results in a less active lipid biosynthesis, a lesser accumulation of lipids and lesser fatty acid oxidation in peroxisomes. It may subsequently lead to expression lowering

of both, catalase and G6PDH at transcriptional level via factors responsible for lipid biosynthesis and fatty acid oxidation, or at posttranscriptional level by free fatty acids.

5. Conclusions and Perspectives

It is now obvious that G6PDH is an important enzyme for supplying cells with NADPH. As a regulatory step of pentose phosphate pathway, G6PDH controls ribonucleotide biosynthesis (since ribose-5-phosphate is formed in this pathway). In bacteria, G6PDH and 6-phosphogluconate dehydrogenase reactions are the main NADPH sources, while eukaryotes possess a battery of other enzymes which may substitute for G6PDH: malic enzyme, NADP-dependent isocitrate and malate dehydrogenases, aldehyde dehydrogenases, transhydrogenase and others. The importance of these NADP-reducing enzymes, including G6PDH, is defined by NADPH roles in cells. These roles are thiol-reduction and direct, and indirect (thiol-mediated) participation in Fe/S cluster biogenesis and heme synthesis, fatty acid and sterol biosyntheses, metal transport and sulfur metabolism. Also, NADPH is involved in many other assimilatory pathways. These roles for NADPH, especially reduction of low and high molecular mass thiols, which detoxify ROS and mediate repair under oxidative stress, characterize G6PDH as an enzyme related to antioxidant defense. However, NADPH is also used by NADPH-oxidases, ROS-producing enzymes, which are essential for immune defense.

Mutations in G6PDH cause sensitivity of *E. coli* to oxidative and related stresses [18, 57]. In the yeast *S. cerevisiae,* such mutations result in lysine and methionine auxotrophies, and in disability to grow on non-fermentable carbon sources [66]. In humans, G6PDH is characterized by hemolytic anemia under certain conditions and can be accompanied by chronic granulomatous disease [2, 6]. Over-expression of G6PDH in *Drosophila* prolongs lifespan [33], while in humans such over-expression can be deleterious and favor carcinogenesis [28, 52, 76]. Abnormalities in regulation of G6PDH activity may lead to increased lipid biosynthesis and obesity [51, 52]. These peculiarities suggest very strict regulation of G6PDH activity. Indeed, G6PDH is an example of housekeeping enzyme which is regulated by multiple ways from transcription of corresponding gene to posttranscriptional and posttranslational levels. These multiple ways of regulation provide very precise response of G6PDH activity to different stimuli. This is also natural in view of simultaneously beneficial and adverse roles of G6PDH for cell and organism survival.

From the time of its discovery, G6PDH structure, functions, and regulation in different organisms were extensively investigated. Today, this enzyme is one of the most studied ones. The reaction catalyzed by G6PDH, its substrates, coenzymes and products, as well as regulation, serve as a model of complex metabolic integration, as we see how many other reactions it affects. Presence of G6PDH in all taxa, makes this enzyme also a good example for studying the evolution of metabolic integration and metabolic pathways [69]. These aspects are just starting to be investigated and require combined approach, involving contemporary methods of biochemistry, molecular and systems biology. The G6PDH reaction is also an example for tissue-specificity of metabolic pathways and their role in providing specific cell functions. In this context, current knowledge on G6PDH has gaps in understanding of complex picture for regulation of its activity and integration with multiple processes in cells. Further studies should be devoted to untangling intertwining between reaction catalyzed by G6PDH and other metabolic pathways, including multiple feedback regulation loops and complex signaling cascades.

REFERENCES

[1] Adam J., Yang M., Soga T., Pollard P.J. Rare insights into cancer biology. *Oncogene*, **33** (20) (2014), 2547–2556.

[2] Agudelo-Florez P., Costa-Carvalho B.T., Lopez J.A., Redher J., Newburger P.E., Olalla-Saad S.T., Condino-Neto A. Association of glucose-6-phosphate dehydrogenase deficiency and X-linked chronic granulomatous disease in a child with anemia and recurrent infections. *Am. J. Hematol.*, **75** (3) (2004), 151–156.

[3] Amemiya-Kudo M., Shimano H., Hasty A.H., Yahagi N., Yoshikawa T., Matsuzaka T., Okazaki H., Tamura Y., Iizuka Y., Ohashi K., Osuga J., Harada K., Gotoda T., Sato R., Kimura S., Ishibashi S., Yamada N. Transcriptional activities of nuclear SREBP-1a, -1c, and -2 to different target promoters of lipogenic and cholesterogenic genes. *J. Lipid Res.*, **43** (8) (2002), 1220–1235.

[4] Amir-Ahmady B., Salati L.M. Regulation of the processing of glucose-6-phosphate dehydrogenase mRNA by nutritional status. *J. Biol. Chem.*, **276** (13) (2001), 10514–10523.

[5] Bayliak M., Semchyshyn H., Lushchak V. Effect of hydrogen peroxide on antioxidant enzyme activities in *Saccharomyces cerevisiae* is strain-specific. *Biochemistry Mosc.*, **71** (9) (2006), 1013–1020.

[6] Beutler E. Glucose-6-phosphate dehydrogenase deficiency: a historical perspective. *Blood*, **111** (1) (2008), 16–24.

[7] Campagne M.V., Thibodeaux H., van Bruggen N., Cairns B., Lowe D.G. Increased binding activity at an antioxidant-responsive element in the metallothionein-1 promoter and rapid induction of metallothionein -1 and -2 in response to cerebral ischemia and reperfusion. *J. Neurosci.*, **20** (14) (2000), 5200–5207.

[8] Desvergne B., Michalik L., Wahli W. Transcriptional regulation of metabolism. *Physiol. Rev.*, **86** (2) (2006), 465–514.

[9] Dieni C.A., Storey K.B. Regulation of glucose-6-phosphate dehydrogenase by reversible phosphorylation in liver of a freeze tolerant frog. *J. Comp. Physiol. B, Biochem. Syst. Environ. Physiol.*, **180** (8) (2010), 1133–1142.

[10] Erasmus D.J., van der Merwe G.K., van Vuuren H.J.J. Genome-wide expression analyses: Metabolic adaptation of *Saccharomyces cerevisiae* to high sugar stress. *FEMS Yeast Res.*, **3** (4) (2003), 375–399.

[11] Fawcett W.P., Wolf R.E. Genetic definition of the *Escherichia coli* zwf «Soxbox» the DNA binding site for SoxS-mediated induction of glucose 6-phosphate dehydrogenase in response to superoxide. *J. Bacteriol.*, **177** (7) (1995), 1742–1750.

[12] Giro M., Carrillo N., Krapp A.R. Glucose-6-phosphate dehydrogenase and ferredoxin-NADP(H) reductase contribute to damage repair during the soxRS response of *Escherichia coli*. *Microbiology (Reading, Engl.)*, **152** (4) (2006), 1119–1128.

[13] Gorrini C., Harris I.S., Mak T.W. Modulation of oxidative stress as an anticancer strategy. *Nat. Rev. Drug. Discov.*, **12** (12) (2013), 931–947.

[14] Gospodaryov D., Lushchak V. Oxidative Stress: cause and consequence of diseases. In: Lushchak V., Gospodaryov D. (Eds.), *Oxidative Stress and Diseases*. InTech (2012), 13–38.

[15] Greenberg J.T., Demple B. A global response induced in *Escherichia coli* by redox-cycling agents overlaps with that induced by peroxide stress. *J. Bacteriol.*, **171** (7) (1989), 3933–3939.

[16] Greenberg J.T., Monach P., Chou J.H., Josephy P.D., Demple B. Positive control of a global antioxidant defense regulon activated by superoxide-generating agents in *Escherichia coli*. *Proc. Natl. Acad. Sci. US.A*, **87** (16) (1990), 6181–6185.

[17] Griffith B.N., Walsh C.M., Szeszel-Fedorowicz W., Timperman A.T., Salati L.M. Identification of hnRNPs K, L and A2/B1 as candidate proteins involved in the nutritional regulation of mRNA splicing. *Biochim. Biophys. Acta*, **1759** (11-12) (2006), 552–561.

[18] Hecker P.A., Leopold J.A., Gupte S.A., Recchia F.A., Stanley W.C. Impact of glucose-6-phosphate dehydrogenase deficiency on the pathophysiology of cardiovascular disease. *Am. J. Physiol. Heart Circ. Physiol.*, **304** (4) (2013), H491–500.

[19] Hong X., Song R., Song H., Zheng T., Wang J., Liang Y., Qi S., Lu Z., Song X., Jiang H., Liu L., Zhang Z. PTEN antagonises Tcl1/hnRNPK-mediated G6PD pre-mRNA splicing which contributes to hepatocarcinogenesis. *Gut*, **63** (10) (2014), 1635–1647.

[20] Hospodarov D.V., Lushchak V.I. Iron metabolism in the yeast. *Ukr. Biokhim. Zh.*, **77** (3) (2005), 5–19. (in Ukrainian)

[21] Imlay J.A. Cellular defenses against superoxide and hydrogen peroxide. *Annu. Rev. Biochem.*, **77** (2008), 755–776.

[22] Jair K.-W., Martin R.G., Rosner J.L., Fujita N., Ishihama A., Wolf R.E. Purification and regulatory properties of MarA protein, a transcriptional activator of *Escherichia coli* multiple antibiotic and superoxide resistance promoters. *J. Bacteriol.*, **177** (24) (1995), 7100–7104.

[23] Jiang P., Du W., Wu M. Regulation of the pentose phosphate pathway in cancer. *Protein Cell*, **5** (8) (2014), 592–602.

[24] Kamerbeek N.M., van Zwieten R., de Boer M., Morren G., Vuil H., Bannink N., Lincke C., Dolman K. M., Becker K., Schirmer R.H., Gromer S., Roos D. Molecular basis of glutathione reductase deficiency in human blood cells. *Blood*, **109** (8) (2007), 3560–3566.

[25] Kletzien R.F., Harris P.K., Foellmi L.A. Glucose-6-phosphate dehydrogenase: a «housekeeping» enzyme subject to tissue-specific regulation by hormones, nutrients, and oxidant stress. *FASEB J.*, **8** (2) (1994), 174–181.

[26] Krapp A.R., Humbert M.V., Carrillo N. The soxRS response of *Escherichia coli* can be induced in the absence of oxidative stress and oxygen by modulation of NADPH content. *Microbiology*, **157** (4) (2011), 957–965.

[27] Kumar C., Igbaria A., D'Autreaux B., Planson A.G., Junot C., Godat E., Bachhawat A.K., Delaunay-Moisan A., Toledano M.B. Glutathione revisited: a vital function in iron metabolism and ancillary role in thiol-redox control: GSH crucial for iron metabolism, minor for redox. *The EMBO Journal*, **30** (10) (2011), 2044–2056.

[28] Kuo W., Lin J., Tang T.K. Human glucose-6-phosphate dehydrogenase (G6PD) gene transforms NIH 3T3 cells and induces tumors in nude mice. *Int. J. Cancer*, **85** (6) (2000), 857–864.

[29] Lama J.L., Bell R.A.V., Storey K.B. Glucose-6-phosphate dehydrogenase regulation in the hepatopancreas of the anoxia-tolerant marine mollusc. *Littorina littorea*. *PeerJ*, **1** (2013), e21.

[30] Lant B., Storey K.B. Glucose-6-Phosphate dehydrogenase regulation in anoxia tolerance of the freshwater crayfish Orconectes virilis. *Enzyme Res.*, **2011** (2011), 524906.

[31] Layer G., Reichelt J., Jahn D., Heinz D.W. Structure and function of enzymes in heme biosynthesis. *Protein Science*, **19** (6) (2010), 1137–1161.

[32] Lee J., Godon C., Lagniel G., Spector D., Garin J., Labarre J., Toledano M.B. Yap1 and Skn7 control two specialized oxidative stress response regulons in yeast. *J. Biol. Chem.*, **274** (23) (1999), 16040–16046.

[33] Legan S.K., Rebrin I., Mockett R.J., Radyuk S.N., Klichko V.I., Sohal R.S., Orr W.C. Overexpression of glucose-6-phosphate dehydrogenase extends the life span of *Drosophila melanogaster*. *J. Biol. Chem.*, **283** (47) (2008), 32492–32499.

[34] Liochev S.I., Fridovich I. Cross-compartment protection by SOD1. *Free Radic. Biol. Med.*, **38** (1) (2005), 146–147.

[35] Ljungdahl P.O., Daignan-Fornier B. Regulation of amino acid, nucleotide, and phosphate metabolism in *Saccharomyces cerevisiae*. *Genetics*, **190** (3) (2012), 885–929.

[36] Longo L., Vanegas O.C., Patel M., Rosti V., Li H., Waka J., Merghoub T., Pandolfi P.P., Notaro R., Manova K., Luzzatto L. Maternally transmitted severe glucose 6-phosphate dehydrogenase deficiency is an embryonic lethal. *EMBO J.*, **21** (16) (2002), 4229–4239.

[37] Lushchak O.V., Rovenko B.M., Gospodaryov D.V., Lushchak V.I. *Drosophila melanogaster* larvae fed by glucose and fructose demonstrate difference in oxidative stress markers and antioxidant enzymes of adult flies. *Comp. Biochem. Physiol., Part A Mol. Integr. Physiol.*, **160** (1) (2011), 27–34.

[38] Lushchak V.I. Glutathione homeostasis and functions: potential targets for medical interventions. *J. Amino Acids*, **2012** (2012), 736837.

[39] Lushchak V. Environmentally induced oxidative stress in fish. In: Abele D., Vazquez-Medina J.P., Zenteno-Savin T. (Eds.) *Oxidative stress in aquatic ecosystems*. Hoboken, NJ: Wiley-Blackwell (2011), 295–307.

[40] Lushchak V.I. Oxidative stress and mechanisms of protection against it in bacteria. *Biochemistry (Moscow)*, **66** (5) (2001), 476–489.

[41] Lushchak V.I., Gospodaryov D.V. Catalases protect cellular proteins from oxidative modification in *Saccharomyces cerevisiae*. *Cell Biol. Int.*, **29** (3) (2005), 187–192.
[42] Ma L., Robinson L.N., Towle H.C. ChREBP*Mlx is the principal mediator of glucose-induced gene expression in the liver. *J. Biol. Chem.*, **281** (39) (2006), 28721–28730.
[43] Manchado M., Michán K., Pueyo C. Hydrogen peroxide activates the soxRS regulon in vivo. *J. Bacteriol*., **182** (23) (2000), 6842-6844.
[44] Maranzana E., Barbero G., Falasca A.I., Lenaz G., Genova M.L. Mitochondrial respiratory supercomplex association limits production of reactive oxygen species from complex I. *Antioxid. Redox Signal.*, **19** (13) (2013), 1469–1480.
[45] Matsui R., Xu S., Maitland K.A., Mastroianni R., Leopold J.A., Handy D.E., Loscalzo J., Cohen R.A. Glucose-6-phosphate dehydrogenase deficiency decreases vascular superoxide and atherosclerotic lesions in apolipoprotein E(-/-) mice. *Arterioscler. Thromb. Vasc. Biol.*, **26** (4) (2006), 910–916.
[46] Mitsuishi Y., Taguchi K., Kawatani Y., Shibata T., Nukiwa T., Aburatani H., Yamamoto M., Motohashi H. Nrf2 redirects glucose and glutamine into anabolic pathways in metabolic reprogramming. *Cancer Cell*, **22** (1) (2012), 66–79.
[47] Moran M., Marin-Buera L., Gil-Borlado M.C., Rivera H., Blazquez A., Seneca S., Vazquez-Lopez M., Arenas J., Martin M.A., Ugalde C. Cellular pathophysiological consequences of BCS1L mutations in mitochondrial complex III enzyme deficiency. *Hum. Mutat.*, **31** (8) (2010), 930–941.
[48] Nakamura M., Bhatnagar A., Sadoshima J. Overview of pyridine nucleotides review series. *Circulation Research*, **111** (5) (2012), 604–610.
[49] Pain J., Balamurali M.M., Dancis A., Pain D. Mitochondrial NADH kinase, Pos5p, is required for efficient iron-sulfur cluster biogenesis in *Saccharomyces cerevisiae*. *J. Biol. Chem*., **285** (50) (2010), 39409–39424.
[50] Palmer M., Chan A., Dieckmann T., Honek J. *Notes to Biochemical Pharmacology*. Wiley, Hoboken, 2013.
[51] Park J., Choe S.S., Choi A.H., Kim K.H., Yoon M.J., Suganami T., Ogawa Y., Kim J.B. Increase in glucose-6-phosphate dehydrogenase in adipocytes stimulates oxidative stress and inflammatory signals. *Diabetes*, **55** (11) (2006), 2939–2949.
[52] Park J., Rho H.K., Kim K.H., Choe S.S., Lee Y.S., Kim J.B. Overexpression of glucose-6-phosphate dehydrogenase is associated with lipid dysregulation and insulin resistance in obesity. *Mol. Cell. Biol*., **25** (12) (2005), 5146–5157.
[53] Puntel R.L., Nogueira C.W., Rocha J.B.T. Krebs cycle intermediates modulate thiobarbituric acid reactive species (TBARS) production in rat brain in vitro. *Neurochem. Res.*, **30** (2) (2005), 225–235.
[54] Ramnanan C.J., Storey K.B. Glucose-6-phosphate dehydrogenase regulation during hypometabolism. *Biochem. Biophys. Res. Commun*., **339** (1) (2006), 7–16.
[55] Salati L.M., Amir-Ahmady B. Dietary regulation of expression of glucose-6-phosphate dehydrogenase. *Annu. Rev. Nutr*., **21** (2001), 121–140.
[56] Saliola M., Tramonti A., Lanini C., Cialfi S., De Biase D., Falcone C. Intracellular NADPH levels affect the oligomeric state of the glucose 6-phosphate dehydrogenase. *Eukaryotic Cell*, **11** (12) (2012), 1503–1511.
[57] Sandoval J.M., Arenas F.A., Vasquez C.C. Glucose-6-phosphate dehydrogenase protects *Escherichia coli* from tellurite-mediated oxidative stress. *PLoS ONE*, **6** (9) (2011), e25573.
[58] Schnell N., Krems B., Entian K.D. The PAR1 (YAP1/SNQ3) gene of *Saccharomyces cerevisiae*, a c-jun homologue, is involved in oxygen metabolism. *Curr. Genet*., **21** (4-5) (1992), 269–273.
[59] Schwartz A.G., Pashko L.L. Dehydroepiandrosterone, glucose-6-phosphate dehydrogenase, and longevity. *Ageing Res. Rev.*, **3** (2) (2004), 171–187.
[60] Semchyshyn H., Bagnyukova T., Lushchak V. Involvement of soxRS regulon in response of Escherichia coli to oxidative stress induced by hydrogen peroxide. *Biochemistry (Moscow)*, **70** (11) (2005), 1238–1244.
[61] Semchyshyn H., Bagnyukova T., Storey K., Lushchak V. Hydrogen peroxide increases the activities of soxRS regulon enzymes and the levels of oxidized proteins and lipids in *Escherichia coli*. *Cell Biol. Int.*, **29** (11) (2005), 898–902.
[62] Sengupta R., Holmgren A. Thioredoxin and glutaredoxin-mediated redox regulation of ribonucleotide reductase. *World J. Biol. Chem*., **5** (1) (2014), 68–74.

[63] Sheftel A.D., Stehling O., Pierik A.J., Elsässer H.P., Mühlenhoff U., Webert H., Hobler A., Hannemann F., Bernhardt R., Lill R. Humans possess two mitochondrial ferredoxins, Fdx1 and Fdx2, with distinct roles in steroidogenesis, heme, and Fe/S cluster biosynthesis. *Proc. Natl. Acad. Sci. USA*, **107** (26) (2010), 11775–11780.

[64] Shelton P., Jaiswal A.K. The transcription factor NF-E2-related factor 2 (Nrf2): a protooncogene? *FASEB J.*, **27** (2) (2013), 414–423.

[65] Sies H. Role of metabolic H_2O_2 generation: redox signaling and oxidative stress. *J. Biol. Chem.*, **289** (13) (2014), 8735–8741.

[66] Slekar K.H., Kosman D.J., Culotta V.C. The yeast copper/zinc superoxide dismutase and the pentose phosphate pathway play overlapping roles in oxidative stress protection. *J. Biol. Chem.*, **271** (46) (1996), 28831–28836.

[67] Stanton R.C. Glucose-6-phosphate dehydrogenase, NADPH, and cell survival. *IUBMB Life*, **64** (5) (2012), 362–369.

[68] Stehling O., Lill R. The role of mitochondria in cellular iron-sulfur protein biogenesis: mechanisms, connected processes, and diseases. *Cold Spring Harbor Perspectives in Biology*, **5** (8) (2013), a011312.

[69] Stincone A., Prigione A., Cramer T., Wamelink M.M.C., Campbell K., Cheung E., Olin-Sandoval V., Grüning N.M., Krüger A., Tauqeer Alam M., Keller Markus A., Breitenbach M., Brindle K.M., Rabinowitz J.D., Ralser M. The return of metabolism: biochemistry and physiology of the pentose phosphate pathway. *Biol. Rev. Camb. Philos. Soc.*, (2014). doi: 10.1111/brv.12140

[70] Storey K.B., Storey J.M. Tribute to P. L. Lutz: putting life on «pause»-molecular regulation of hypometabolism. *J. Exp. Biol.*, **210** (10) (2007), 1700–1714.

[71] Talukdar I., Szeszel-Fedorowicz W., Salati L.M. Arachidonic acid inhibits the insulin induction of glucose-6-phosphate dehydrogenase via p38 MAP kinase. *J. Biol. Chem.*, **280** (49) (2005), 40660–40667.

[72] Thomas D., Surdin-Kerjan Y. Metabolism of sulfur amino acids in *Saccharomyces cerevisiae*. *Microbiol. Mol. Biol. Rev.*, **61** (4) (1997), 503–532.

[73] Tong W.H., Rouault T.A. Metabolic regulation of citrate and iron by aconitases: role of iron-sulfur cluster biogenesis. *Biometals*, **20** (3-4) (2007), 549–564.

[74] Verdegem D., Moens S., Stapor P., Carmeliet P. Endothelial cell metabolism: parallels and divergences with cancer cell metabolism. *Cancer Metab*, **2** (2014), 19.

[75] Walsh C.M., Suchanek A.L., Cyphert T.J., Kohan A.B., Szeszel-Fedorowicz W., Salati L.M. Serine arginine splicing factor 3 is involved in enhanced splicing of glucose-6-phosphate dehydrogenase RNA in response to nutrients and hormones in liver. *J. Biol. Chem.*, **288** (4) (2013), 2816–2828.

[76] Wang J., Yuan W., Chen Z., Wu S., Chen J., Ge J., Hou F., Chen Z. Overexpression of G6PD is associated with poor clinical outcome in gastric cancer. *Tumour Biol.*, **33** (1) (2012), 95–101.

[77] Wasserman W.W., Fahl W.E. Functional antioxidant responsive elements. *Proc. Natl. Acad. Sci. U.S.A.*, **94** (10) (1997), 5361–5366.

[78] Winterbourn C.C., Benatti U., De Flora A. Contributions of superoxide, hydrogen peroxide, and transition metal ions to auto-oxidation of the favism-inducing pyrimidine aglycone, divicine, and its reactions with haemoglobin. *Biochem. Pharmacol.*, **35** (12) (1986), 2009–2015.

[79] Wood T.I., Griffith K.L., Fawcett W.P., Jair K.W., Schneider T.D., Wolf R.E. Interdependence of the position and orientation of SoxS binding sites in the transcriptional activation of the class I subset of *Escherichia coli* superoxide-inducible promoters. *Mol. Microbiol.*, **34** (3) (1999), 414–430.

[80] Zhang X., Krause K.H., Xenarios I., Soldati T., Boeckmann B. Evolution of the ferric reductase domain (FRD) superfamily: modularity, functional diversification, and signature motifs. *PLoS ONE*, **8** (3) (2013), e58126.

[81] Zheng M., Wang X., Templeton L.J., Smulski D.R., LaRossa R.A., Storz G. DNA microarray-mediated transcriptional profiling of the *Escherichia coli* response to hydrogen peroxide. *J. Bacteriol.*, **183** (15) (2001), 4562-4570.

Address: Dmytro Gospodaryov, Vasyl Stefanyk Precarpathian National University, 57, Shevchenko Str., Ivano- Frankivsk, 76018, Ukraine.
E-mail: dmytro.gospodaryov@gmail.com.
Received: 27.02.2015; **revised:** 05.04.2015.

Господарьов Д.В. Мало досліджені ролі глюкозо-6-фосфатдегідрогенази. *Журнал Прикарпатського університету імені Василя Стефаника*, **2** (1) (2015), 25–37.

Огляд розглядає певні аспекти реакції, яку каталізує глюкозо-6-фосфатдегідрогеназа (Г6ФДГ), у живих організмів усіх таксонів: від бактерій до людини. Особливий наголос зроблено на ролі Г6ФДГ у гомеостазі заліза та ліпогенезі. Також висвітлені прооксидантна та антиоксидантна ролі Г6ФДГ і декілька відомих на даний час механізмів регуляції Г6ФДГ.

Ключові слова: глюкозо-6-фосфатдегідрогеназа, НАДФН, супероксид, тіол, залізо-сірчані кластери, глутатіон.