

Editorial

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Association of Glucose-6-Phosphate Dehydrogenase Deficiency with Ocular Diseases

Suofu Qin*

Retinal Disease Research, Department of Biological Sciences, Allergan Inc., RD3-2D, 2525 Dupont Drive, Irvine, CA 92612-1599, USA

Glucose-6-phosphate dehydrogenase (G6PD, EC1.1.1.49) is expressed in all tissues where it is the first and rate-limiting enzyme of the pentose phosphate pathway (PPP) [1] that consists of the oxidative and non-oxidative branches and usually works at 1-2% of its maximal potential in healthy subjects due to the high level of nicotinamide adenine dinucleotide phosphate (NADPH). The G6PD gene is wildly expressed, especially higher in red cells because PPP is the only pathway for generating reducing capacity in the erythrocyte. Active G6PD in human cells is a dimer or tetramer in a pH-dependent equilibrium, and each monomer is composed of 515 amino acids [2]. The G6PD activity is regulated by the levels of NADP⁺ for sufficient supply of NADPH through stimulating as a substrate the activity of the enzyme directly and stabilizing the enzyme in the proper conformation [3]. G6PD deficiency (lower activity due to the numerous point mutations) is classified into four classes by the WHO according to the remaining activity of wild-type G6PD activity. These are described as: class I is <1%; class II is <10%; and class III is 10~60% of normal G6PD function. Class IV is 60~100% that is considered as normal G6PD activity [4]. G6PD deficiency is the most common enzymopathy in human, affecting over 400 million people in the world.

G6PD deficiency has been well known to be associated with malaria protection in tropical and subtropical regions because of *Plasmodium*induced suicide of host erythrocytes where G6PD deficiency renders erythrocytes susceptible to *Plasmodium*-caused oxidative stress [5]. The other recognized clinical manifestation of G6PD deficiency is hemolytic anemia of varying severity induced by certain drugs and fava beans [2]. However, more evidences are correlating G6PD deficiency with other diseases as G6PD is a critical metabolic enzyme that regulates many physiological processes. Thus, this editorial discusses an evolving field where G6PD deficiency alters risk of ocular diseases.

G6PD and Redox Balance

Oxidation of glucose 6-phosphate into 6-phosphogluconolactone by G6PD forms the first NADPH and subsequent oxidative decarboxylation of 6-phosphogluconic acid by 6-phosphogluconic dehydrogenase produces the second NADPH in the oxidative branch of PPP. NADPH is not only used as a reducing agent in synthesis of lipids and in detoxification reactions, but also is the limiting substrate for glutathione reductase and thioredoxin reductase, the enzymes that regenerate GSH and reduced thioredoxin for detoxifying reactive oxygen species (ROS) [6]. ROS are chemically reactive molecules containing oxygen such as superoxide $(O_2^{\bullet-})$ and hydrogen peroxide (H_2O_2) . Oxygen is fundamental to cellular respiration as an acceptor of electron transfer. Incomplete one-electron reduction of oxygen produces O_2 that is dismutated to H_2O_2 by superoxide dismutase. H₂O₂ can be converted into the highly reactive hydroxyl radical. O₂⁻⁻ reacts with nitric oxide (NO⁻) to form peroxynitrite (ONOO⁻), a potent oxidant. In cells, the levels of ROS are contingent on cellular antioxidant activity. ROS produced at a low level by the electron transport chain play a physiological role in the regulation of cell signaling, proliferation, and differentiation. Elevated production of ROS and / or diminished antioxidant levels exhibit higher oxidative damage to macromolecules including DNA, dys-regulate signaling pathways, and alter cell metabolisms [7]. Rising levels of NADH is a major factor leading to increased mitochondrial ROS production [8].

Additionally, NADPH-dependent oxidases including the NADPH oxidases (Noxs) and the NO[•] synthases [9] are another major source of intracellular ROS. Decrease in the supply of NADPH will reduce capacity of Nox-dominant cells to produce ROS. Mice knocked out for G6PD die *in utero* or have severe abnormalities in the placenta [10], as a consequence of oxidative stress. In contrast, G6PD-deficient mice have lower production of Nox-derived O_2^{+-} [11]. Thus, decreasing G6PD activity could be protective or damaging effect as NADPH has an antioxidant (GSH regeneration) and a pro-oxidant (Nox-derived ROS) activity.

Increased Risk for Cataract, Retinopathy and Pterygium in G6PD-Deficient Subjects

Insufficient supply of NADPH in G6PD-deficient subjects can cause significant deleterious effects on cellular physiology and cellular survival as decreased synthesis of GSH. Accordingly, G6PD deficiency may be sufficient to cause disease. The incidence of G6PD deficiency in the lens of 32 Sicilian subjects (15 males and 17 females) is significantly higher (p<0.001), suggesting that G6PD deficiency is a risk factor for cataract [12]. This is further supported from an independent study in Cukurova, Turkey that the incidence of lens G6PD deficiency in 52 cataract patients is 52%, significantly higher than that in agematched controls [13]. A small study of 19 G6PD-deficient patients suggests that decreased G6PD activity may predispose to development of proliferative diabetic retinopathy as the incidence of proliferative diabetic retinopathy is more prevalent in G6PD-deficient patients (28%, p<0.005 vs. G6PD-sufficient) [14]. In another study of 54 children with sickle retinopathy, researchers found that G6PD deficiency is more common in patients with proliferative retinopathy though not statistically significant [15]. Moreover, analysis of 123 pterygium patients with Sardinian ancestry suggests that G6PD deficiency is a risk factor for the development of pterygium [16]. These studies show that subjects with G6PD deficiency are under risk for certain ocular diseases.

*Corresponding author: Suofu Qin, Retinal Disease Research, Department of Biological Sciences, Allergan Inc., RD3-2D, 2525 Dupont Drive, Irvine, CA 92612-1599, USA, Tel: 714-246-4132; Fax: 714-246-5578; E-mail: ginsuofu@hotmail.com

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Decreased Risk for Retinal Vein Occlusion and Ischemic Optic Neuropathy in G6PD-Deficient Subjects

NADPH shortage can also reduce production of NADPHdependent oxidase-derived ROS, thereby protecting tissues or organs from oxidative damage, on the other hand. Determination of erythrocyte G6PD activity in 140 patients with ischemic optic neuropathy and 280 age-and gender-matched controls from Sardinia, Italy shows that G6PD deficiency is found in 7 (5%) patients and 34 (12.1%) control subjects [17]. The incidence is significantly lower (p=0.02) in patients than in controls. Evaluation of erythrocyte G6PD activity from 194 patients with retinal vein occlusion and 896 age- and gender-matched subjects also reveals that the incidences of G6PD deficiency are 4.7% (21 patients) and 11.9% (107 controls), respectively [18]. The difference between cases and controls is statistically significant (p<0.005). How G6PD deficiency de-risks for development of ischemic optic neuropathy and retinal vein occlusion in Sardinian population is unclear. Whether reduction in NADPH oxidase activities is linked to the decreased risk of these two ocular disorders remains to be confirmed.

Perspectives

Several critical issues remain to be addressed for efficient management of the subjects with G6PD deficiency. First, rapid, cost-effective, and quantitative high throughput screening of G6PD activity is not yet available. Fluorescent spot test is a simple, fast, and popular method detecting G6PD deficiency when the blood spot fails to fluoresce under ultraviolet light [2]. However, the fluorescent spot test is unreliable for the detection of heterozygous females and is semiquantitative. The development of a cheaper, faster, and quantitative assay for the G6PD is mandatory, allowing a quicker translation of G6PD investigations from basic research to a diagnostic setting. Second, not all people with G6PD deficiency are symptomatic although G6PD deficiency is a predisposing factor. What co-factor(s) lead to the development of various diseases, remains to be answered. One case report shows that an Army Ranger has developed central retinal vein occlusion following primaquine administration [19]. The other reports development of vitroretinal hemorrhages upon ingestion of fava beans [20]. Identifying unknown symptomatic co-risk factors will greatly help the management of the subjects with G6PD deficiency.

Finally, except avoidance of oxidative stressors, there is no good treatment for the subjects with G6PD deficiency. Antioxidant supplement with vitamin E might have little benefit for the treatment of G6PD deficiency [21]. Anti-oxidative approach has been tested to prevent hemolysis in G6PD-deficient red blood cells [22]. More effort is needed to identify the key biological processes associated with disease biology in G6PD-deficient subjects. The progress in understanding disease mechanisms and developing high throughput screening assay will significantly help the diagnosis and treatment of G6PD-deficient patients.

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