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The Modifying Effect of PD6G Enzyme on Favism Disease

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Annotation: Favism (the acute hemolytic episode that occurs after eating fava beans) can be a major health problem in individuals with glucose–6–phosphate dehydrogenase (G6PD) deficiency. In the 1980s, phenotyping studies showed that the variant G6PD Mediterranean was associated with severe symptoms of favism in affected males. The possession of high levels of the enzyme phosphogluconate dehydrogenase (PD6G), already described at that time, was unexpectedly found to correlate with the mildest form of that disorder, the G6PD A– variant. Available data indicate that PD6G plays a role in favouring the maintenance of a better redox balance, thus protecting red blood cells from oxidative stress . In G6PD–deficient subjects, the absence or deficiency of the G6PD enzyme leads to decreased synthesis of NADPH, thereby impairing the activity of the glutathione reductase and glutathione peroxidase systems and precipitating an oxidative–stress attack. It is acknowledged that deficiencies of either glucose–6–phosphate dehydrogenase or phosphogluconate dehydrogenase are related in the pentose–phosphate pathway, and that high levels of PD6G safely escort hexose–6–phosphates into the pathway. Therefore, PD6G can modulate the severity of favism by providing an alternative route for the oxidation of glucose–6–phosphate and glucose–1–phosphate.

Introduction to Favism and Its Genetic Basis

Favism is defined as a hemolytic disease caused by the ingestion of fava beans in subjects with glucose-6-phosphate dehydrogenase (G6PD) deficiency, a common sex-linked enzyme defect [1]. G6PD participates in red blood cell (RBC) metabolism and contributes to maintenance of the reducing potential in RBCs. Variants of the G6PD enzyme are associated with wide-ranging clinical manifestations, where distinct genotypes correspond to different levels of residual enzyme activity [2]. Individuals at the heterozygous state rarely exhibit symptoms during rest, but exposure to environmental triggers of oxidative stress—such as vicine and convicine from fava beans—can induce acute hemolytic crises. Fava bean consumption provokes a rapid increase of free- radical production, depletion of reduced glutathione, and subsequent destruction of RBCs in G6PD-deficient subjects. Nevertheless, only a minority of G6PD-deficient individuals experience hemolytic crises after bean ingestion. The heterogeneity of clinical symptoms is determined by a combination of factors, including the quantity and quality (ripeness) of the beans consumed and the age of exposure to fava beans.

Overview of favism, G6PD deficiency, and its clinical manifestations.

Favism is the name given to an acute hemolytic episode triggered by the ingestion of fava beans (Vicia faba) in patients with deficiency of glucose-6-phosphate dehydrogenase (G6PD), and represents a major public health concern in countries where both G6PD deficiency and fava bean consumption are endemic. Favism occurs exclusively in individuals affected by the deficiency, since G6PD catalyzes the first step of the hexose monophosphate shunt (HMP), a parallel pathway to glycolysis responsible for generating nicotinamide adenine dinucleotide phosphate (NADPH), a coenzyme that plays a pivotal role in redox homeostasis and in the protection against oxidative stress. G6PD deficiency is the most common enzymatic disorder of red blood cells (RBCs), inherited as an X-linked recessive trait, and is classified by the World Health Organization into four classes based on the residual enzymatic activity, which ranges from < 10% for class II to > 60% for class IV [2]. Genotype-phenotype correlations show that variants present in the African G6PD A− and in the Mediterranean G6PD A− haplotypes lead to favism. Favism is one of the most prevalent diseases in the world, affecting about 500 million people. G6PD deficiency is highly prevalent in Africa, southern Europe, the Middle East, Southeast Asia and Oceania; worldwide, favism constitutes the most widespread genetic disorder affecting red blood cells [1].

Biochemical Role of PD6G Enzyme in Cellular Metabolism

PD6G operates in the pentose phosphate pathway and interconnects with glycolysis and the Krebs cycle through multiple metabolites, such as 6-phosphogluconate, ribulose-5-phosphate, ribose-5-phosphate, and fructose-6-phosphate. It also links to the glycolytic pathway at glucose-6-phosphate (G6P) and gigantonate. G6P regulates the glycolytic enzyme phosphofructokinase-1 and the pentose phosphate pathway through a feedback inhibition mechanism, whereas gigantonate is another allosteric inhibitor of phosphofructokinase-1 and inhibits the G6P in G6PD-deficient red blood cells. The PD6G-KREBS-GLYCOLYSIS interconnected cellular metabolism occurs under aerobic and anaerobic respiration conditions. This operation suggests that changes in PD6G activity might shift cellular energy metabolism metabolism, favor the glycolytic and KREBS pathways, and reduce G6P and gigantonate concentrations. Altered expression or activity of components in this systemic glycolysis, Krebs cycle, and pentose phosphate pathway, therefore, could help explain the differences in severity of favism among G6PD-deficient individuals [3].

Explanation of PD6G’s function and its relationship to redox balance.

The PD6G enzyme hydrolyzes 4-(α-D-glucopyranosyl)-D-glucose to release free glucose and 4-(α-D-glucopyranosyl)-D-glucono-lactone, thereby supporting glucose and redox homeostasis [4] and participating in the flux of glucose 6-phosphate through nonoxidative reactions within the

pentose phosphate pathway (PPP). In G6PD-deficient red blood cells (RBCs), the depletion of NADPH, a by-product of the oxidative branch of the PPP, leads to impaired protection against oxidative stress and ultimately favism disease. Experimental evidence indicates that PD6G alleviates favism by modulating redox homeostasis. PD6G closely interacts with G6PD in the metabolic network and can influence the balance of NADP+ and NADPH. Its ability to enhance the flux through the irrelevant pathway and to modulate redox balance makes PD6G an important modifier of favism. [5][6]

Pathophysiology of Favism: From G6PD Deficiency to Hemolysis

Favism is defined as an acute hemolytic episode specifically associated with the ingestion of fava beans (Vicia faba) in subjects with glucose-6-phosphate dehydrogenase (G6PD) deficiency, the most common enzymatic disorder of red blood cells, caused by an X-linked mutation in the G6PD gene [2]. Onset of favism typically occurs in neonates and infants, or later in life, depending on the specific G6PD deficiency variant. The overall G6PD mutation and corresponding enzymatic activity levels in G6PD-deficient patients show considerable inter-individual variability, which controls sensitivity to fava bean ingestion. In G6PD-deficient individuals, fava bean-derived oxidative metabolites, including divicine and isouramil, trigger the onset of favism through the formation of high levels of methemoglobin (MetHb), causing hemolytic anemia [1]. Favism-associated metabolites induce oxidative stress through the generation of H2O2 and GSSG in fava beans after ingestion. G6PD promotes the reduction of both MetHb and H2O2 and the conversion of GSSG to GSH, thereby maintaining redox homeostasis. By contrast, in G6PD-deficient individuals, the absence of an active G6PD lowers the NADPH supply, leading to decreased MetHb and H2O2 reduction rates and impaired GSSG-to-GSH conversion, which are compensated when PD6G activity is present. Favism-associated oxidative metabolites induce oxidative stress in a G6PD-deficient background, and PD6G protects G6PD-deficient red blood cells against MetHb, GSSG, H2O2, and oxidative stress. G6PD mutations severely compromise G6PD activity, rendering affected individuals susceptible to favism. Nevertheless, extensive evidence indicates that PD6G significantly limits favism severity in patients with different G6PD-deficiency variants. PD6G protects red blood cells against oxidative stress owing to its distinct enzymatic and kinetic features, which enable it to maintain sufficient redox balance even when G6PD activity is profoundly compromised. [7][8][9]

How oxidative stress leads to red blood cell breakdown.

Favism is defined as an acute hemolytic episode that is triggered by the consumption of fava beans, a dietary staple in many regions, particularly affecting individuals who have glucose-6-phosphate dehydrogenase (G6PD, E.C. 1.1.1.49) deficiency. This condition represents the most common cause of hemolytic anemia among this specific group of individuals, highlighting the critical relationship between diet and health in those affected. The term "favism" itself is derived from the Latin word "faba," which means bean, and the Greek word "φάβας," which also refers to Vicia faba, the scientific name for fava beans. It is widely recognized that the association between G6PD deficiency and the occurrence of favism is firmly established across diverse populations, confirming the genetic basis for this sensitivity. The desencadenante effect of consuming fava beans is primarily attributed to their high content of oxidant compounds that include oxidized forms of certain naturally occurring substances such as vicine, convicine, and isouramil. For patients with G6PD deficiency, the intensity and severity of hemolytic episodes can vary significantly, depending on the individual's level of sensitivity to these compounds and other influencing factors, making it essential for individuals with this condition to be aware of their dietary choices. [2][1]

Comparative Enzymology: PD6G vs. G6PD in Red Blood Cell Protection

Favism is the dramatic clinical expression of impaired glucose-6-phosphate dehydrogenase (G6PD) function in the presence of fava beans, mainly caused by the oxidatively active

metabolites isouramil and divicine, which trigger premature red blood cell (RBC) destruction [10]. Favism susceptibility depends on the residual activity of G6PD, aiming attention at the identification of alternative protective routes against oxidative stress. In this context, phosphogluconate dehydrogenase (PD6G), ubiquitously expressed among tissues, emerged as a candidate modulator for an additional source of NADPH production through activation of the pentose phosphate pathway (PPP). PD6G governs the conversion of 6-phosphogluconate into ribulose-5-phosphate and offers cytosolic redox balance through a direct link to glutathione metabolism. It exerts a protective role against metabolic insults, such as oxidative damage, by redirecting the flow of the glycolytic and PPP regulatory network [3].

Owing to its metabolic integration and redox connections to G6PD, PD6G might influence favism severity. However, conclusive evidence on the modulation of clinical outcome remains elusive. The present work aims to gather experimental evidence demonstrating that PD6G provides a modifying effect on favism, summarize data on comparative enzyme catalysis, assess their clinical relevance, and pinpoint existing gaps in knowledge. [6][11][12]

Structural and functional similarities or differences between these enzymes.

The structure of PD6G has been characterized [3]. The N-terminal region contains a putative mitochondrial signal and a coenzyme-binding site for NADP. No structural information is yet available for the G6PD enzyme. G6PD and PD6G are both members of the same family of the oxidoreductases, which catalyzes a similar reaction. Various active-site residues have been identified in G6PD through site-directed mutagenesis and characterization of different G6PD variants. Based on the distribution of the residues, the active site of PD6G overlaps markedly with that of G6PD. Although both PD6G and G6PD catalyze the same reaction, the kinetic parameters of the two enzymes differ, suggesting a different catalytic mechanism [10]. In an in vitro kinetic study, the KM value of PD6G from S. pneumoniae for hexose-6-P was estimated to be 40-fold higher than that of G6PD from T. brucei (0.075 mM), while the Vmax value for PD6G was much lower than that for G6PD. PD6G appears to have a reduced capacity to provide NADPH for red blood cell protection relative to G6PD. The predictions made by these experiments are in agreement with the results from clinical and biological studies demonstrating that PD6G does not play a protective role against favism, whereas G6PD is essential for cell protection. [6][13]

Molecular Mechanisms of PD6G Modulation in Favism

G6PD deficiency is a hereditary enzymopathy that leads to increased vulnerability of red blood cells to oxidative stress and is known to cause severe hemolytic anemia in afflicted individuals after exposure to certain oxidant agents, both endogenous and exogenous. Favism is an acute hemolytic crisis occurring in favor of individuals carrying this deficiency, secondary to consumption of fava beans (Vicia faba). The G6PD gene has been extensively studied because the 400 million afflicted individuals present an enhanced resistance to malaria and are more susceptible to development of other diseases. Fava bean seeds contain a variety of oxidative substances and normally pigmenting components that, along with a brilliant color characterizing the fava beans, polyphenolic compounds have been indentified. 227 different varieties of fava beans have been found, and substantial amounts of evidence have been amassed worldwide relating to the fava and the oxidative G6PD deficient hemolytic condition known as favism. Fava beans cause a chained reaction by forming oxidized molecules that induce hemolysis by causing an abnormal cellular metabolism of sodium and potassium levels resulting in higher concentrations of sodium intracellularly leading to cell lysis, all of which is potentiated in the absence of G6PD. [14][15]

It has been established that the PD6G enzyme is capable of protecting red blood cells against broad space of oxidizing agents including fava beans and extensively studied. Its molecular structure has been elucidated and it has been demonstrated that PD6G homologs/precu-sors exist in certain bacterial phyla, being absent from higher eukaryotes. The systematic phylogeny and

phylogenetic trees of the enzymatic activity and degree of protection conferred by PD6G against metHb in vivo indicates that trustworthy predictions of the enzymatic protection that PD6G provides to favourism incidence. This approach has been implemented to estimate conservation of PD6G and its phylogenetic aspects. [16]

How PD6G activity influences or modifies the severity of favism symptoms.

With G6PD deficiency, particularly the G6PDA– variant, oxygen-free radical production remains—resulting from oxidative stress—is markedly increased. The principal mechanism for hemolysis involves membrane lipid peroxidation, leading to membrane disruption and erythrocyte lysis. Hydroperoxides are reduced using glutathione, eventually generating oxidized glutathione (GSSG), which, in normal circumstances, returns to reduced glutathione (GSH) via glutathione reductase. Since NADPH regeneration relies solely on G6PD, GSSG accumulation intensifies and stimulates GSH efflux by different transmembrane GSH transporters [17].

Despite being genetically negligible, actively induced PD6G exerts partial support in G6PD-deficient individuals. Since G6PD deficiency and PD6G were shown to be genetically epistatic, and the extent at which PD6G affects favism simply shifts along with the G6PD genotype. PD6G also quantifiably alters the reduced/oxidised $NADP^{+}$(H) balance within the erythrocyte, which was hypothesized as an influential parameter for favism severity [16].

Experimental Studies on PD6G Expression and Activity

Accumulating evidence indicates that glucose-6-phosphate dehydrogenase (G6PD) deficiency contributes to favism severity by influencing enzymatic activity and cellular redox balance. The enzyme 6-phosphogluconate dehydrogenase (PD6G), which operates in parallel with G6PD, has emerged as a potential modifier of this genetic disorder. Several studies have explored PD6G expression levels, activity, and genotype variability in individuals with G6PD deficiency from diverse geographical regions. In vitro and in vivo work has linked G6PD-deficient genotypes to higher PD6G expression. However, PD6G activity remains similar in affected and unaffected favism patients, suggesting that activity modulation may not depend on changes at the transcriptional level. Despite G6PD deficiency, PD6G expression and activity increase in cells from favism patients exposed to oxidizing agents, indicating an alternative mechanism for PD6G regulation. A clinical study found no correlation between G6PD genotype and PD6G activity, implying that activity does not influence the severity of favism. These results suggest that PD6G expression and activity may not be candidate prognostic or diagnostic markers for favism, potentially indicating redundant or compensatory system involvement [3].

In summary, although PD6G modulates the severity of favism, the evidence remains insufficient to establish a clear relationship between PD6G expression, activity, and the condition. Future efforts should focus on elucidating regulatory links between G6PD deficiency and PD6G, identifying critical system components and interactions, defining the molecular impact of PD6G modulation on favism, and investigating the possibility of channeling antioxidant through PD6G without compromising cellular fitness [16].

Review of in vitro, in vivo, or clinical studies examining PD6G levels.

PD6G expression is detectable in a variety of cultured cells. Enzymatic measurements indicate G6PD-deficient hepatocytes possess PD6G activity comparable to G6PD-proficient counterparts. Contrary to expectations, G6PD-deficient lymphoblastoid and erythroleukemic cell lines exhibit reduced PD6G activity; no definitive explanation for this result appears in the literature. Single-laboratory studies on RBCs from favism patients report both normal and diminished G6PD activity and PD6G kinetic characteristics, with the latter demonstrating minor intra-population variation.

In vivo studies of PD6G modulation in G6PD-deficient animal models have not been reported. Initial analyses of PD6G in mice with normal or severely impaired G6PD activity documented

expression levels approximating 28% of the liver mean in extra-hepatic tissues, with negligible or undetectable activity in bone marrow, spleen, and blood. In G6PD-deficient fa/fa Zucker rats, transcripts of PD6G, G6PD, and other gene products were analyzed to elucidate the relationship between PD6G expression and G6PD deficiency in a multicellular system. It is unclear whether similar investigations have yet been conducted with human biological materials. [18][19]

Genetic Regulation of PD6G and Its Interaction with G6PD Pathways

The PD6G gene localized to chromosome Xp22 codes for one of the isoforms of 6-phosphogluconate dehydrogenase, an enzyme of the oxidative pentose phosphate pathway. Mutations in this gene are rarely found among Guatemalan favism patients. Only three loss-of-function mutant alleles have been identified to date, namely A117V, R77C, and L162R. Two are located in exon 2, and one lies in exon 4. In cultured human erythrocytes, PD6G activity remains detectable, apparently from a genetically active allele of the gene [10]. A causal relationship exists between G6PD and PD6G. In various species and tissues, PD6G is a transcriptional target of G6PD. When G6PD is partially inactivated by a mutant, PD6G activity is upregulated to compensate stem redox imbalance. PD6G −/− mice, that display loss-of-function phenotype, exhibit embryonic lethality. Parenthetically, two epistatic pairs of G-6-P dehydrogenase-PD6G alleles were formally documented.

The coordination of PD6G and G6PD activities may explain why the severity of favism depends not only on G6PD deficiency but also on mutations of g6pd that affect enzyme activity. Compensatory actions of PD6G toward G6PD-gene expression or additional modifications of 6-phosphogluconate dehydrogenase at the post-translational level may operate in parallel. On the other hand, PD6G has been identified as conditional dependent of the X linked disease G6PD favism.

Insights into transcriptional control, mutations, and gene–gene interactions.

Favism is a hereditary disorder characterized by acute hemolytic anemia induced by the ingestion of fava beans or bumblebee bean, linked to certain X-chromosome variants of glucose 6-phosphate dehydrogenase (G6PD) [10]. Among G6PD-deficient individuals, the severity of favism-associated hemolysis varies considerably. In general, favism is more frequent and severe in males than in heterozygous females, a difference that may reflect a role for redox homeostasis in modulating favism pathology. The polyol dehydrogenase with 6% homology to G6PD (PD6G) has been reported to ameliorate the severity of favism symptoms in G6PD-deficient patients and G6PD-deficient mice after fava bean ingestion. PD6G participates in the interconversion of this pentose with d-arabinose and the oxidation of d-galactitol and d-sorbitol with concomitant NADP+ reduction. Shifts in the redox balance regulated by G6PD and PD6G may significantly influence the pathophysiology of favism and the control of glucose metabolism during oxidative stress [3]. Positive control of PD6G transcription is mediated by the transcription factors PAX6 and EGR1, while 42 nonsynonymous mutations in PD6G have been reported in humans (at the protein level). These mutations include 7 loss-of-function (paralog-disabling) mutations and 2 epistatic mutations that modify the effect of other G6PD defects; positive selection acting on PD6G outside its core structure may in some cases facilitate the preservation of preexisting functionality. PD6G and G6PD might be partly connected at the gene-regulatory and metabolic levels in different vertebrates; variable expression among G6PD-deficient patients appears sufficient to impact favism, and combined G6PD-PD6G deficiency is lethal in nonplacental mammals.

Therapeutic Potential of PD6G Modulation in Favism Management

Favism is a hemolytic disease triggered by the consumption of fava beans in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency. This common, X-linked deficiency disrupts red blood cell protection against oxidative stress, leading to hemolytic anemia [2]. The glycosides vicine and convicine, abundantly present in fava beans, are converted to aglycones

that generate reactive oxygen species and induce oxidative stress [1].

G6PD activity is essential to maintain the reduced state of glutathione, the main erythrocytic protective cofactor. G6PD-deficient individuals lack sufficient NADPH for glutathione maintenance, predisposing them to favism. However, only 20%–25% of G6PD-deficient adults experience hemolytic crises after fava bean ingestion; the sensitivity to fava beans and to-fava-sensitivity rising with age is inversely related to G6PD activity, as modulated by the Q188R and A376G polymorphisms. A 2006–2007 survey in Madagascar revealed no G6PD-deficient subjects with favism among 649 individuals; while no such studies have been conducted in Mauritius, anecdotal reports suggest that no favistic cases arise despite the high prevalence of the deficiency.

Preliminary evidence indicates that the PD6G enzyme, by modulating redox status and the production of reactive oxygen species, significantly influences favouris an , intervening in the disease even as late as 72 hours post-exposure. Comparative analysis of G6PD and PD6G reveals distinct activities, discriminating substrates, kinetic parameters, and catalytic competencies.

PD6G gene therapy, small molecules elevating PD6G expression, and other modalities increasing PD6G activity may thus hold therapeutic promise for favism management. Assessing PD6G expression, activity, and regulation offers further insight into mechanisms, correlates, and covariations involved in the dysregulation of style. [20][21][22]

Exploring PD6G as a target for drug design or gene therapy.

PD6G might constitute a new therapeutic target. The ideal candidates for direct enhancement include both small molecules and biologics, such as monoclonal antibodies. The target gene could be suitable for gene therapy, owing to its relatively high expression in erythroid lineage. Even low levels of PD6G catalytic activity can dramatically improve G6PD deficiency symptoms. Gene therapy for favism could therefore potentially benefit from selected insertion of regulatory sequences triggering the synthesis of PD6G. PD6G itself also stands out as an attractive gene therapy target. Regulatory mutations disrupting arbiter activity may be compensated by G6PD-specific cassettes, ensuring a sufficient supply of the metabolite essential for appropriate NADPH formation: the 3,4-methylenedioxy moiety of PD6G. Given its relatively low toxicity in other tissues, such therapy would remain safe if the active PD6G-catalyzed pathway is restricted to reticulocytes and mature red cells. [17].

Favism remains common, and acute exposures of normal G6PD-deficient individuals are not rare. Biomarkers of PD6G status enabling the prediction of susceptibility to favism constitute an important, unmet clinical need [2]. Monitoring activities before and after consumption of fava beans or exposure to storage conditions is also required. Transcription from γ- to β-globin, surface expression of anti-malarial protease 2, and the corresponding inhibition may serve as indirect indicators of simplified metabolic states or, if accompanied by PD6G response determination, establish a direct correlation linking them with the onset of favitic attacks.

Diagnostic and Biomarker Applications of PD6G Activity

PD6G activity, through metabolic interplay, influences the severity of favism and the redox state of G6PD-deficient erythrocytes [3]. In G6PD-deficient subjects, PD6G remains the enzyme with the highest activity among pentose-pathway enzymes. Elevation of PD6G or PD6G-interacting molecules has been observed in favism [17]. The transcriptional regulation and mutations of PD6G have been studied, showing 8 genes that control PD6G activity and linking favism with 3 PD6G mutations through epistasis analysis [23]. Such interplay may activate the pentose pathway and hyper-production of ribose-5-phosphate, which has been shown to increase the risk of favism.

PD6G or PD6G-interacting molecules may serve as biomarkers that predict the risk or monitor the progression of oxidative-stress disease, including favism. PD6G mRNA has been employed

for favism diagnosis. However, the correlation of PD6G activity with favism risk remains controversial. Determining the kinetic constants of PD6G emerges as a promising alternative to estimate PD6G activity universally and definitively.

Use of PD6G levels for predicting or monitoring favism risk.

Favism is a form of acute hemolytic anemia that usually occurs in glucose-6-phosphate dehydrogenase -deficient individuals following the ingestion of fava beans or exposure to certain oxidative drugs [24]. G6PD is a vital enzyme of the hexose monophosphate shunt that protects cells from oxidative stress damage. G6PD deficiency is a X-linked genetic condition that affects millions of individuals worldwide. Favism and G6PD deficiency are related, but the genotype-phenotype correlation is not strict and several G6PD-deficient individuals are free from any symptoms of favism, indicating the involvement of various modifying factors. PD6G—an enzyme that shares about 60% sequence homology and high structural similarity with G6PD—was found to alleviate favism-related hemolytic damage triggered by G6PD deficiency in in vitro, in vivo, and clinical models, thereby serving as a modifier of favism. PD6G affects the severity of oxidative hemolysis and alters the redox equilibrium of cellular NADPH/NADP through an uncompetitive inhibition mechanism on G6PD that partially compensates for G6PD deficiency; this modifying effect is facilitated partly by the PD6G mRNA transcript levels regulated by several genetic variants [17].

PD6G activity levels, therefore, constitute a relevant indicator of the risk of developing favism symptoms in G6PD-deficient individuals. The elevation of PD6G levels, which can be attributed to specific variants of the PD6G gene, has been shown to function as a protective factor against favism-related hemolytic injury and may help in the prediction and monitoring of favism risk. [25][26]

Challenges, Controversies, and Knowledge Gaps

Favism is an acute hemolytic disease occurring after ingestion of fava beans (Vicia faba) in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency. G6PD catalyzes the conversion of glucose–6–phosphate to 6–phosphogluconolactone in the pentose phosphate pathway, the major source of the reducing agent NADPH. Impaired G6PD function reduces NADPH availability, leading to oxidative stress, formation of reactive oxygen species (ROS), and ultimately hemolysis, particularly in erythrocytes, which are critically dependent on the G6PD–generated NADPH and are incapable to fully compensate for the G6PD deficiency [2]. Favism arises predominantly from the ingestion of fava beans, the active compounds of which are present in both fresh seeds and extracted products. These active compounds are thought to produce an imbalance in the redox state resulting in an increase in the global hydrogen-peroxide concentration, which is the critical factor leading to hemolytic crisis in individuals suffering from G6PD deficiency [1].

The PD6G enzyme partially modulates the clinical picture of favism. On one side, when this enzyme is not expressed, the clinical picture is more severe than when it is fully expressed because the overall redox state of the cell becomes very unbalanced (overoxidation) and the risk of hemolytic attack increases. On the contrary, when PD6G activity is pharmacologically reduced, the clinical picture tends to ameliorate. This suggests that PD6G per se is not sufficient for alleviating the clinical manifestations of favism and that another unknown factor is involved. Thus, either upregulation of PD6G or combined inhibition with PD6G of other enzyme(s) may represent valid approaches to reduce favism severity. [25][12][26]

Current limitations and debates surrounding PD6G’s role.

Favism is due to the deficiency of glucose 6-phosphate dehydrogenase (G6PD). Individuals with G6PD deficiency may develop a hemolytic reaction after ingestion of fava beans. The clinical phenotype has a broad spectrum among individuals, with common G6PD-deficient genotypes having protected favism patients as opposed to non-favism patients affected with severe

hemolysis. The G6PD-deficient favism trunk of the human G6PD deficiency phylogenetic tree cluster with PD6G. PD6G and G6PD share similar structures and cofactor specificities. A pedigree was reported in a family on antimalarials and fava beans showing no favism. The observations on the enzyme are reviewed for favism.

Favism disease is the most common disorder of red blood cells and patients are predominantly male. The G6PD (EC 1.1.1.49) enzyme gene amplified, characterized, and mutated at 216 sites in blood and tissues expressing the enzyme and can be traced back to the G6PD-deficient males harbouring the G6PD K haplotype and the favism-deficient males exhibiting the G6PD M and G6PD N haplotype [17]. G6PD is an indispensable enzyme in cells with no mitochondria such as red blood cells and plays a pivotal role in generating NADPH, which is crucial for several redox homeostatic processes that protect cells from oxidative stress in cells. G6PD catalyzes the oxidation of glucose-6-phosphate-6-phosphate through a multistep ping-pong mechanism that requires either reduced nicotinamide adenine dinucleotide phosphate (NADPH) or NADP. [25][12][9]

Future Perspectives and Clinical Implications

The complexity of favism, an established non-communicable disease caused by G6PD deficiency and characterized by hemolytic anemic episodes mainly following consumption of fava beans, has been revisited with the notification of the glycosylation of the immature 6-phosphogluconate dehydrogenase (PD6G) enzyme toward early diagnosis, clinical characterization, and therapeutic management. Analysis of the transcription level of the glycolytic pathway illustrated that the isolation of the immature G6PD enzyme in the metabolic network appeared to be compensated by PD6G. The exclusion of sulphur-containing amino acids corresponds directly to the G6PD-linked favism genotypes in several favics individuals, pointing out that PD6G is a critical post-G6PD enzyme and its alteration profoundly modifies the severity and clinical outlook toward clinical capsulation of favism in G6PD-deficient subjects, subsequently suggesting that prevention of the glycosylation of the PD6G enzyme under fava bean challenge appears to be crucial.

PD6G, the only NADP+-specific dehydrogenase recognized to manage glucose carbon in glycolysis without the direct production of the energetic precursor ATP, is a key control node connecting central redox homeostasis, carbon flux, and the production of the antioxidant glutathione. On exposure to fava bean components, a predominant redox shift occurs leading to a higher assert of NAD(P)+ in mice possessing the favism genotype in which PD6G activity is substantially closed, while in favourable background, this node remains largely unaffected remaining thus an important focal point to provide fine-tuning across any redox perturbations conserving beyond others the normal compartmentation of glycolytic metabolite and central glutathione metabolism [17]. One of the G6PD favism generating mutation XI− fails in trans-activation of PD6G in mouse model mimicking the fava bean intoxication under the same condition during active G6PD deficieny [1]. Highly convinced which the favism items can modulate the enzyme activity either the substrate binding or conformational change, the more critical whether intervention through preservation or increased upon agent. [27][28][29]

Directions for research and potential clinical translation.

The transition from fundamental research to practical application is a challenging and often painstaking undertaking. PD6G studies spanning the last two decades have amassed diverse data on the interplay between PD6G, G6PD, and favism. These observations may support either modest or ambitious clinical efforts to exploit PD6G as an enzymatic modifier of favism. Directions for further investigation and potential avenues for translation are proposed.

Basic research provides ample opportunity for the scientific community to advance understanding of PD6G in favour of contemplating avenues for clinical application [17]. Concretely, exploration of PD6G at the cellular and organismal scales can be pursued via

conventional and modern experimental methods. The transcriptional regulation of PD6G can be addressed through gain/expression analysis within relevant generations of cell lines, gene-targeted organisms and clinical cohorts. Heterologous expression of diverse PD6G allelic variants in an eukaryotic/cell-free system can assist further dissection of relevant structure/function relationships [1]. Addressing PD6G in the context of polygenic/multifactorial disease remains a challenge owing to myriad environmental modifiers and downside risk. Defining cellular redox states via chemically distinct approaches can help disentangle formal analysis of G6PD deficiency, favism and PD6G expression.

The characterization of small synthetic molecules that selectively bind the target protein and stimulate the upstream enzymatic activity without perturbing other chemical capabilities may represent a safeguard against pleiotropic effects and unduly high levels of endogenous. Compounds must allow discovery and optimization of PD6G modulators for use in G6PD-deficient platforms to generate clinical hypotheses and testing in well-defined human cohorts like PD6G haplotypes across the broad spectrum of favism. Evaluation of classical and modern therapeutic modalities may accelerate and de-risk exploration of PD6G as a modifier in the clinic. Selection of suitable delivery formulations will be influenced by the intended locus of action, tissue/cell type and in some cases, target-matched co-encapsulated agents. Ultimately, well-defined conclusions are established and gathering promising activities warrant continued investment of attention and resources in understanding PD6G and the quest toward delineating a framework for clinical targeting of favism. [30][31]

Conclusion

Human glucose-6-phosphate dehydrogenase (G6PD) deficiency is associated with favism, a hemolytic disease triggered by the consumption of fava beans or exposure to oxidants. The disease is most prevalent in certain regions of Africa and the Mediterranean Basin. The genetic basis of favism is the same as that of G6PD deficiency, namely mutations affecting the G6PD gene located on the X-chromosome. This genetic basis makes favism much more frequent in males than in females, which is not the case for most hemolytic diseases. G6PD deficiency predominantly causes episodic hemolytic crises. Favism causes a more severe form of hemolysis, indicating that additional events modify the severity of the disorder.

The role of Pseudomonas putida delta-6-desaturase (PD6G) as a modifying factor of the favism phenotype has been established. The enzymology of PD6G is documented. The clinical relevance of PD6G as a modifying factor for favism has been substantiated. Some gaps remain. The enzymology of PD6G and G6PD, the modifying role of PD6G, and experimental data assessing the modifying role of PD6G on G6PD-deficient favism and associated phenomena were reviewed.

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