Glutathione S-transferase Activity in Diagnostic Pathology

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Abstract

Glutathione S-transferase (GST) is a generic term that describes a class of proteins involved in phase-II detoxification of endogenous compounds and xenobiotics. Regulation and function of GSTs have influences on cell growth, oxidative stress, as well as disease progression and prevention. Although not routinely assayed in clinical laboratories, the present review highlighted the application of GST activity in diagnostic pathology. Human GSTs are divided into three main families, namely, the cytosolic, mitochondrial and membrane-bound microsomal GSTs. The expression of GST isoforms in biologic systems may well be of relevance from a clinical and toxicity standpoint and applies in the renewed efforts in eradication and control of parasitic infections. A survey of frequency of polymorphism and measure of GST activity among human population groups are reliable and valuable diagnostic tools. The reliability of GST activity in diagnostic pathology is underscored in pathologic conditions/disorders whose etiologies are associated with overwhelming levels of oxidative stress and failure of GST-mediated detoxification mechanisms.

Keywords: Diagnosis; Glutathione S-transferases; Isoforms; Pathology; Polymorphisms

Introduction

Glutathione S-transferase (GST; EC: 2.5.1.18) is a generic term that describes a class of proteins involved in phase-II detoxification of endogenous compounds and xenobiotics [1]. GST isoenzymes exhibit differential but overlapping substrate specificity, in which the catalytic efficiency of the individual isoenzyme dictates the extent to which biotransformation of the substrate occurs [2-5]. The GST-mediated detoxification pathway ensures cellular protection from environmental insults and oxidative stress, though it has also been implicated in cellular resistance to drugs [5-11]. For instance, overexpression of GSTs in the endothelium serve to protect soft tissues against oxidative damage from aldehydes such as 4-hydroxyxynonal (4-HNE) [12] and neuroprotection of photoreceptors is connected with GST-mediated reduction of oxidative stress in retinal explants from rd1/rd1 mice [13].

Much attention was focused on thiol-mediated antioxidant/ detoxification proteins since the 1970s [14]. Early reports showed that GSTs isolated and characterized from rat and human liver [3,15-18], pigeon, locust gut, housefly and other sources [16] have common properties to bind to reduced glutathione (GSH) and wide variety of hydrophobic compounds. The structural dimensions of the GSTs have been exhaustively described [14]. Overall, regulation and function of GSTs have influences on cell growth, oxidative stress, as well as disease progression and prevention [5]. GSTs are divided into two distinct family members, the membrane-bound microsomal and cytosolic family members. The expression or activities of specific GST isoforms in various biological systems are closely associated with different clinical conditions and toxicity outcomes. Thus, the frequency of polymorphism or measurement of GST activity among human population groups are reliable and valuable diagnostic tools. Although not routinely assayed in clinical laboratories, the present review highlighted the application of GST activity in diagnostic pathology because of the indispensable role of the enzyme in cellular functional integrity.

Evidence acquisition

Scientific search engines such as PubMed, Pubget, Medline, EMBASE, Google Scholar, ScienceDirect and SpringerLink were used to retrieve online publications from 1969 to 2015. Keywords such as ‘Plasmodium’, ‘malaria’, ‘glutathione detoxification’, ‘ligandins’, ‘oncology’ ‘polymorphisms’, ‘metabolic disorders’, ‘hepatobiliary’ etc. were used to collate relevant articles. The results were then cross-referenced to generate a total number of 125 references cited in this review.

Functions of glutathione S-transferases

The functions of GSTs have been classified into two general categories [19,20]. As intracellular binding proteins [2,21,22], GSTs function on a broad scale in solubilizing and transport of substances such as the extracellular functions of albumin described elsewhere [23,24]. The GST from rat liver, designated as transferase B, has been shown to be identical to the bilirubin binding protein or ‘ligandins’ [25]. Although ligandins have high affinity for endogenous compounds such as bile acids, haemin, bilirubin, fatty acids and steroids [16,18,22], whose conjugates are eventually sequestered [26], the bound GSTs are devoid of catalytic processing and do not form glutathione conjugates with their substrates [18,27]. Another specific protective role of GST as ligandin is the specific binding of intra-erythrocyte GSTP1-1 isoform to Jun-kinase, a pro-apoptotic enzyme that becomes inactive when bound to GST [26,28].

The second major function is the protection of cellular components [29,30] by the preferential reaction of electrophilic agents with GSH through the enzymatic action of GSTs, and thereby prevents the reaction of electrophiles with cellular nucleophiles. The enzyme may also detoxify certain extremely reactive substances by direct covalent binding to electrophilic agents [1,22,31]. For the most part, GSTs catalyze the conjugation of electrophilic groups of hydrophobic drugs and xenobiotics to form glutathione-thioethers [32]. These thioethers are converted to mercapturic acid by the sequential actions of γ-glutamyl transpeptidase, depeptidase and N-acetylase [2,15,33] prior to the eventual elimination of the hydrophilic conjugates.

Reactive oxygen and nitrogen species (ROS/RNS) can alter the

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structure and/or function of number proteins by their selective modification of proteins such as enzymes, receptors, structural proteins, transcription factors and transport proteins and may also alter a variety of protein-protein interactions. Additionally, raised cellular ROS/RNS levels promote peroxidation of structural and particulate lipids such as those present in biomembranes and lipoproteins, which form the molecular basis of several pathologic conditions. The GSTs participate in protecting the cell against deleterious actions of ROS/RNS by promoting redox homeostasis through neutralization of excess reactive electrophiles, whose chemical actions elicit numerous signaling cascades associated with cell proliferation, inflammatory responses, apoptosis and senescence [14]. In parasitic infections, e.g. malaria, GST is a component of the thiol-mediated antioxidant detoxification systems of Plasmodium that are required for survival of the malarial parasite in hypertoxic intracellular environment it encounters during its development in mammalian and insect hosts [7,34-36]. Also, physicochemical analyses of the gastrointestinal blood-feeding nematode *Haemonchus contortus* showed that the parasite harbors GST of high-affinity for hematin, which represented the parasite adaptation to blood or tissue feeding from the host [37]. Helminth GSTs participate in detoxification of lipid hydroperoxides and carbonyl cytotoxins produced by oxygen-reactive intermediates [38]. Accordingly, *Plasmodium falciparum*, *H. contortus* and helminth GSTs have been suggested to be attractive targets for new anti-parasitic drugs and vaccine discovery [37-39].

**Molecular dimensions of glutathione S-transferases**

Human GSTs are divided into three main families, namely, the cytosolic, mitochondrial and membrane-bound microsomal GSTs [5,8]. For instance, the cytosolic human GSTP1-1 is a monodimeric intracellular protein of about 46 kDa expressed in different organs and cell types [26]. Specifically, the molecular mass of the cytosolic GSTs monomers are in the range of 22-29 KDa and exhibit activity over a wide variety of substrates with considerable overlap [1,2,4]. Each monomer contains an active site with two sub-sites: a less conserved H site for binding to specific hydrophobic substrates and a highly conserved G site for binding to GSH [14]. The general mammalian cytosolic GSTs encompass dissimilar dimeric isoenzymes within molecular mass of 45-55 KDa, which have been assigned to at least four generic classes, namely, α-, µ-, ω- and θ-GSTs [2,3,26,41,42] in addition to the K- ω-, δ-GSTs [5,43], whereas the membrane bound microsomal GSTs are component of another classified proteins, the so called membrane-associated proteins in eicosanoid and glutathione metabolism (MAPEG) [44-46]. The MAPEG entities are involved in endogenous metabolism of leukotrienes- and prostaglandins-derived mediators of pain, fever, and inflammation as well as in biotransformation and detoxification of electrophilic substrates [14,46]. Using electron crystallography, the molecular dimensions of microsomal GST has been established as well as identification of critical amino acid residues that are responsible for intramolecular or intermolecular contacts in stabilizing the active site, which applies in interpreting the structure–function relationship for similar MAPEG entities [46].

**Isoforms**

The human liver cytosolic GST classes are α-, β-, γ-, δ-, ε- [25] and Ζ-GSTs [47]. These six classes of GST originate from six different chromosomes but share ~30% sequence identity [14]. GST isoforms have cell specific distribution (e.g. GSTA1 in hepatocytes and GSTP1 in the biliary tract of the human liver) [48]. The GSTP1 isoform exists in the human erythrocytes [49], which is different from the GSTs present in the human liver [1,17]. Although, all GST isoymes have two domains and similar topologies, <10% of the protein is strictly conserved [14]. The occurrence of genetic polymorphisms in the various classes of cytosolic GSTs have been described and linked to the prevalence of incidences of cancers, parasitic infections, diverse pathologic conditions and disorders [8,10,14,50-52]. For instance, polymorphisms in the GSTP1 gene arise from nucleotide transitions that change codon 105 from Ile to Val and codon 114 from Ala to Val, thus generating four GSTP1 alleles: wild-type GSTP1*A (Ile105→Ala114), GSTP1*B (Val105→Ala114), GSTP1*C (Val105→Val114) and GSTP1*D (Ile105→Val114) [14,53]. Evaluation of three GST isoforms-GSTM1, GSTP1 and GSTT1 in patients presenting acute respiratory distress syndrome showed an association between GST1- null, GSTM1- and GSTT1-double null polymorphisms with increased incidence of mortality [10]. Additionally, individuals with the GSTM1-null or GSTT1-null genotypes display absence of enzymatic activity and are believed to be at higher risk to cytotoxic effects of a wide spectrum of xenobiotics and carcinogens [54]. Structural analyses of these GST variants showed steric alteration at the substrate-binding site of the enzyme without affecting the GSH binding site, which correspondingly implies that GSH binding affinity are not affected, whereas significant alterations at the substrate binding domain occur [55]. As a consequence of GST polymorphisms, enzymatic activities of the GST variants are significantly altered.

**Parasitic infections**

The level of parasite GST activity serves to define the capability of the organism to withstand anti-parasitic drugs. For instance, in chloroquine-resistant strains of rodent (*Plasmodium berghei, P. yoelii*) and human malarial parasites, GST activity was significantly raised when compared with the sensitive strains and was directly related to drug pressure on resistant parasite [56]. Alterations in serum or plasma levels of GST activity and its GSH cofactor are diagnostic of parasitic infection in susceptible individuals [57,58]. According to Sohal et al., [57] the mean activity of GST in serum and plasma of patients infected with *P. vivax* were less (6.43 and 5.65 IU/L respectively) than the corresponding healthy subjects (11.65 and 10.09 IU/L respectively). They further noted that the decreased GST activity served to protect the host erythrocytes against the invading malarial parasite by up-regulating oxidative defense mechanisms. In the same vein, previous reports have shown that antioxidants such as GSH, catalase and α-tocopherol were lower in patients with malaria [51,59] or visceral Leishmaniasis [58] than the control groups. Consequently, low levels of plasma GST activity may elicit the accumulation of ROS/RNS because of decreased antioxidant scavenging capacities with attendant membrane lipid peroxidation and oxidation of haemoglobin to methaemoglobin [58]. According to Chikezie et al., [60], outcome of comparative study of GST activity of human erythrocyte genotypes infected with *P. falciparum* suggested that GST activity was a reliable biomarker and possesses promising rational for diagnostic potential in malaria.

In another investigation, Kavishe et al., [51] reported that polymorphisms in GST genes were associated with susceptibility and severity *P. falciparum* malaria in Cameroon population. In their study, the frequencies of polymorphisms in GSTM1, GSTT1, and GSTP1 in DNA of 138 children from Cameroon were analyzed using multiplex polymerase chain reaction (mPCR) assay, whereas that of GSTP1 was done using polymerase chain reaction–restriction fragment
length polymorphism (PCR-RFLP) assay. The findings indicated that
malarious subjects with complications were more often of the GSTM1-
null genotype (58–64%) as against those with uncomplicated malaria
(32%), a difference that was statistically significant ($x^2=6.7; p=0.05$;
$x^2=3.5; p=0.031$). Thus, there was an established relationship between
the frequencies of GST polymorphisms and levels of severity and
complication of malaria in children.

Oncology

The GST isoforms conjugate GSH to electrophilic carcinogens and
there are incontrovertible evidence that underscores the relationship
between GST polymorphism and incidence of development of cancers
of the gastrointestinal tract, ovaries, prostate, and esophagus in selected
mammalian population [9,61-67]. Furthermore, the level of expression
of GST could provide useful diagnostic parameter in carcinoma
of the breast [68] and bladder [69,70]. Evidence from molecular
epidemiological studies showed that individual susceptibility to cancer
is mediated by both genetic and environmental factors. For instance,
individuals who have both GSTT1- and GSTM1-null genotypes are
more predisposed to acute myeloid leukemia [71] as well as oral
leukoplakia risk as a result of carcinogenic intermediates derived from
or generated during habitual chewing of betel quid/tobacco [72,73].

In oncology, the GSTP1 isoform, which is the most ubiquitous
and prevalent GST in non-hepatic tissues, are present in raised levels
in many tumors, particularly, that of the ovarian, non-small cell lung,
breast, colon, pancreas and lymphomas as well as in wide range of drug
resistant cell lines [14,74]. In specific terms, Bostwick et al., [9] reported
differential expression of GSTA1, GSTM1 and GSTP1 isoforms in
benign prostate, prostatic intraepithelial neoplasia, and prostatic
adenocarcinoma. The study observed that consistent reduction or loss
of expression of all subclasses of GST could engender the progression
of prostatic neoplasia from benign epithelium to high-grade prostatic
intraepithelial neoplasia and carcinoma. Another investigation
according to Chen and Lin, [63] showed that raised levels of GSTA1,
GSTM1 and GSTP1 activities confirmed oral epithelial dysplasias
(OEDs) and squamous cell carcinomas in human. Specifically, total
GST activities of the three isoforms were significantly elevated in mild
OED, moderate OED, severe OED and squamous cell carcinoma when
compared with that from normal buccal mucosa [63]. They further
noted that GSTP1 was the major isoform in the cytosolic fraction of
oral mucosa and severity of OED was connected with the development
squamous cell carcinoma, which appeared to increase correspondingly
with increased level of GSTP1 activity.

In another study, Naidu et al., [64] described the implication of total
GST activity levels and GSTP1 protein expression in paired samples of
colorectal cancer, adenoma and normal mucosa from a total of thirteen
patients using spectrophotometric methods. The study showed that
GST activity was significantly raised in both colorectal cancer and
adenomas when compared with normal colonic tissue-an indication
that raised levels of GST activity may serve as a useful diagnostic
index for colonic neoplasia in humans. Conversely, in the reports of
Szarka et al., [61] significant low levels of GST activity was noted in
blood lymphocytes from high-risk colorectal cancer individuals when
compared with blood lymphocytes from control individuals ($p < \sigma = 0.004$).
However, no association was observed between the frequency of
GSTM1 phenotype and risk of colorectal cancer and high-risk
individuals unable to express GSTM1 had lower levels of GST activity
than those from control subjects ($p < \sigma = 0.006$) [61]. There are
evidence to suggest an association between GSTM1-null genotype and
increased risk of gastric cancer [67]. Using case-control study approach
involving PCR-based assays, Casson et al., [66] hypothesized that
polymorphisms of microsomal epoxide hydroxylase and GST genes
modulated the susceptibility to esophageal adenocarcinoma (EADC)
associated with smoking, which showed a strong statistical association
between smoking and risk for EADC in individuals.

There are contradictory reports on the use of GST activity as a
diagnostic index in the monitor and ascertaining therapeutic benefits
following treatment of ovarian cancer patients. Wrigley et al., [62] used
immunohistochemistry and Western blot methods to evaluate the
correlation between GSTA1, GSTM1 and GSTP1 isoforms activities in
association with clinicopathological features and response to treatment
in ovarian cancer, in which they noted that none of the GST isoenzyme
levels were significantly correlated with response to treatment. In
a related study, serum GST activity of untreated patients with malignant
ovarian tumors was significantly raised when compared with those
of healthy individuals and patients with benign ovarian tumors [65].
From their study, Akçay et al., [65] further suggested that a monitor of
GST activity was important in diagnostic and therapeutic approach to
detection and treatment of ovarian cancer.

Hepatobiliary damage

Patients with hepatoacellular damage exhibit elevated plasma
GST activity [75,76]. Although serum GSTA1 activity is a sensitive
biomarker of liver injury [77,78], studies according to Thorburn et al., [79]
showed that it was not useful in ascertaining the level of liver
inflammation in chronic hepatitis C infection, though the data
may be of more value than ALT in monitoring response to treatment
with α-interferon. Nevertheless, reports of Yukihiko et al., [77] noted
that the degree of correlation between serum GST and ALT or AST
was high in acute hepatitis, with ALT or AST exceeding 200 IU/L
in fulminant hepatitis, primary hepatoma and gall stones, whereas
in chronic hepatitis and liver cirrhosis the correlation was low.
Furthermore, serum GST exhibit shooter half-life than ALT or AST in
the blood, which suggest new and unique information for the diagnosis
of acute liver diseases. A recent clinical survey by Weng et al., [80]
established the association between drug hepatotoxicity and daily dose,
liver metabolism and lipophilicity of oral medications. They noted
that high oral dose of drugs and extensive hepatic GST mediated drug
metabolism is independent but not synergistic risk factor for oral
drug to induce hepatic injury, which correlated with significant plasma
ALT/AST elevation. The findings have further confirmed the potentials
of applying GST activity in prediction and monitoring of drug toxicity.
Nevertheless, earlier reports by Rattenbury et al., [81] had noted that
measurement of GSTRI isoform in serum using radioimmunoassay
technique may be a better predictor of hepatic dysfunction in cystic
fibrosis than conventional liver function tests.

Diabetes mellitus and metabolic disorders

The GSTs, in concert with antioxidant systems, modulate
oxidative stress associated with diabetes mellitus (DM). For instance,
mitochondria-specific GSTKisoform has also been implicated in obesity,
diabetes and related metabolic disorders [5]. Conversely, GSTP1-
isoleucine/valine and valine/valine alleles, alone or in association with
GSTM1-null and GSTT1-present genotypes, does not influence the risk
of susceptibility to development of metabolic disorders [82]. Although
the studies according to Sanil et al., [83] did not find a significant
association between GSTM1 and GSTP1 polymorphisms and carotid
atherosclerosis, the GSTT1-null genotype and GSTT1-null/GSTM1-
null haplotype might be potential determinants of susceptibility to
advanced atherosclerosis in patients with T2DM.
Using a 2-year change of the common carotid intima media thickness (CCA-IMT), which was measured using B-mode ultrasonography, de Waart et al., [84] suggested that smokers who expressed the GSTM1-null genotype, and thus lacking this functional detoxifying enzyme, developed progression of atherosclerosis in a significantly (p=0.02) increased rate when compared with smokers with GSTM1-positive genotype. A related study by Park et al., [85] showed that GSTTL1-null genotype might be connected with carotid atherosclerosis related to rheumatoid arthritis in Korean postmenopausal women without histories of smoking. Furthermore, the protective role of GST activity against vascular cell injury was reported by Xu et al., [86], in which they established that hGSTA4-4 overexpression protected the integrity of vessel wall epithelium from oxidative injury, as earlier mentioned [12], and attenuated transplant arteriosclerosis.

Studies have shown that silencing the GSTA4 gene resulted in mitochondrial dysfunction, as was also observed in mice that exhibited GSTA4-null genotype, which contributed to insulin resistance in Type 2 DM (T2DM) [5]. Accordingly, mPCR assay of GST isoforms has established a relationship between GST gene polymorphism and DM [87-89]. In specific instance, the GSTM1-null/GSTTL1-null genotypes contributed to the clinical course of T2DM patients and increased susceptibility to T2DM in Brazilian population [88], whereas GSTTI1-present genotype conferred protection against the development of a T2DM [90-92]. Another study by Amer et al., [87] showed that the frequency of the Val allele in exon 5 of the GSTP1 gene in patients with T2DM was 15.2% as against that observed in healthy controls (9.6%); and was statistically significant (p=0.03) when compared with Ile allele carriers. They further noted that the presence of GSTP1 heterozygous mutant allele Ile/Val in Egyptian population was more common in subjects with T2DM than in the control group (30.4% and 19.2%, respectively; p=0.02). Recent findings of Rasheed et al., [89] have corroborated the association of GSTM1 and GSTTI1 gene polymorphisms with T2DM in Iraqi patients.

Cross-sectional study by Velladath et al., [91] showed a weak positive correlation between erythrocyte GST activity and HbA1c concentration in diabetic patients (r=0.239, p=0.089). Although the study appeared to suggest that GST activity is associated with formation of HbA1c in diabetic patients, chronicity of the disease along with treatment modalities that might have played a significant role in the outcome of the study [91].

Reproductive system disorders

The GSTM1- and GSTTI1-null genotypes have been associated with male infertility [94] and female infertility [95,96]. The high frequency of homozygotes GSTM1 gene deletion among patients with endometriosis suggests a possible contribution of environmental toxins in the pathogenesis of this disease due to the absence or low activity of GSTM1 [50]. Many environmental and genetic etiological factors that are responsible for the occurrence of early pregnancy loss have been controversially discussed. However, the frequencies of polymorphisms in phase-I drug metabolizing enzymes (cytochrome P450 genes) and phase-II detoxification enzymes (e.g., GST genes) may contribute to the development of pre-eclampsia [96]. The occurrence of the GSTP1b-1b genotype – a non-functional GSTM1 or GSTTI1 allele has been linked to relatively lower GSTP1 activity with consequential impaired placental detoxification capability, which represents a risk factor for recurrent early pregnancy loss [97]. In concord with earlier investigation by Suryanarayana et al., [98], studies according to Polimanti et al., [99] and Nair et al., [100] reported that the expression of GSTA1- and GSTM1-positive/null genotypes in Italian women and GSTTI1- and GSTM1-null genotypes in Indian women, respectively were connected with the incidence of reoccurring pregnancy loss. The findings particularly noted that the -69T allele in the GSTA1 gene may be considered as a predisposing factor of recurrent miscarriage.

Chandra et al., [101] recently reported that there was a definite association between maternal GSTTI1- and GSTM1-null genotypes and higher incidence (p=0.001) of fetal growth restriction (IFGR), which correlated with fetal weight. They further noted that cumulative levels of GST activity in mothers giving birth to IFGR babies was about 50% of the values found in the control group (p<0.001). Measurement of GST activity in neonates is a useful biomarker of oxidative stress and evaluation of protective treatment trials at birth [102].

Finally, GST activity is a reliable biomarker of oxidative stress in liver, kidney and testes, and more specifically, a measure to ascertain acute toxic effects of zearalenone, which is a non-steroidal estrogenic mycotoxin produced by several species of Fusarium, on reproductive system of adult male Swiss albino mice [104]. A related study by Quinn et al., [105] showed that resistance of mouse liver to aflatoxin B1 (AFB1) could be traced to single constitutive GST isoenzyme with a relatively high activity toward DNA-binding metabolites of AFB1.

Alcoholism and substance abuse

GSTM1 genotype in human population may be associated with a greater susceptibility to alcohol-induced spermatogenesis disorders, whereas the occurrence of GST M1-null and GSTP1-null genotypes are associated with alcoholic liver disease [106-109]. Expectedly, alcohol-dependent subjects exhibited significantly lower (p<0.001) GST activity in blood and saliva when compared with control subjects due to elevated oxidative stress and impairment of antioxidants in alcoholism [110]. Nevertheless, the investigation revealed a significant increase (p<0.001) in GST activity, with near control values, following alcohol withdrawal.

According to the reports of La Vignera et al., [111], the frequency of GSTM1 genotype in heavy drinkers with normal spermatogenesis differed from that of corresponding moderate drinkers, whereas the frequency of GSTM1 genotype in heavy drinkers with disorders of spermatogenesis was similar to moderate drinkers with or without disorders of spermatogenesis. Additionally, since the study of Pajarinen et al., [106] noted that >20% of heavy drinkers had normal spermatogenesis; it was an indication that the GSTM1 genotype exerts a protective effects on alcohol-induced spermatogenesis disorders.

Studies involving the role GSH and redox signaling in substance abuse showed that chronic use of drugs, such as cocaine and methamphetamine lead to the formation of ROS/RNS and alterations in GSH and redox homeostasis [112]. As expected, GST activity exerted protective role during substance abuse and intoxication. The hazardous effect of heroin intoxication on different regions of the brain was evaluated using real time polymerase chain reaction (RT-PCR) in the reports of Gutowicz et al., [113], in which they noted that the protective effect of GST was observed to be lower in brain stem than in brain cortex or hippocampus.
Renal injury and uremia

Localization of GSTA1 isoform in specific parts of the proximal renal tubule, which is readily released into the urine following injury, is used as an excellent biomarker for proteinuria [114]. Over-expression of GST by >50% in erythrocytes of patients with chronic renal failure and uremia [20,26,115,116] and early diagnosis for uremia-related complications [117], which have received immense attention and documentation. Galli et al. [20] reported that over-expression of GST activity was the consequence of an increased expression of the protein rather than a kinetic modulation of the enzyme. In these studies, the significant increase in erythrocyte GST activity in pre-dialysis patients showed a positive correlation with the disease severity. Furthermore, the stable level of erythrocyte GST activity, during the life span of the erythrocyte, provides a suitable yardstick for assessing the adequacy of different dialytic techniques [20,26]. One of such evaluation was carried out in complementary to a mathematical model that takes into account the urea clearance in a single hemodialysis session \([Kt/V_\text{urea}}\) parameter for classification of kidney disease outcomes quality initiative [118]; where \(K = \text{dialyzer clearance of urea}, t = \text{dialysis time and } V = \text{volume of distribution of urea}\) in the course of depurination against large and small toxins in uremic patients [26].

Rheumatoid arthritis

Meta-analysis of epidemiological surveys involving PCR based assays showed that there was a relationship between GSTM1, GSTT1 and GSTP1 polymorphisms and pathogenesis of rheumatoid arthritis in Asian or European population [119-122]. On the contrary, case-control study approach using amplification refractory mutation system-PCR and mPCR assays revealed that only the GSTM1-null and GSTT1-null genotypes alongside GSTP1 (Ile105→Val114) polymorphism display low GST detoxification capacity, which are potential risk factors that influence susceptibility to rheumatoid arthritis and impact on the outcome of the disease [124]. The therapeutic response to non-steroidal anti-inflammatory drugs (e.g., D-penicillamine) in rheumatoid arthritis may be influenced by GST polymorphisms. Studies according to Layton et al. [125] showed that patients who possess the GSTM1*0-GSTM3*A haplotype are significantly less likely to show beneficial response to D-penicillamine.

Conclusion

The expression of various GST isoforms in biologic systems is of relevance from clinical and toxicity standpoints and applies in renewed efforts in the eradication and control of parasitic infections. The present review showed that a survey of frequency of polymorphism and a measure of GST activity among human population groups are reliable and valuable diagnostic tools in ascertaining the prevalence and susceptibility to various forms of pathology by individuals who express such protein genotypes. Additionally, the reliability of GST activity in diagnostic pathology is underscored in pathologic conditions/disorders whose etiologies are associated with overwhelming levels of oxidative stress and failure of GST-mediated detoxification mechanisms.

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