GSTP1 and cancer: Expression, methylation, polymorphisms and signaling (Review)

JIAN CUI[1], GUOQING LI[1,2], JIE YIN[1,2], LINWEI LI[3], YUE TAN[1], HAORAN WEI[1], BANG LIU[1], LIHONG DENG[1], JIALU TANG[1], YONGLIN CHEN[1] and LAN YI[1,2]

[1]Hengyang Medical College, Institute of Cytology and Genetics, Key Laboratory of Ecological Environment and Critical Human Diseases Prevention of Hunan Province Department of Education, University of South China; [2]Hunan Province Cooperative Innovation Center for Molecular Target New Drug Study; [3]Department of Laboratory, The Second Affiliated Hospital, University of South China, Hengyang, Hunan 421001, P.R. China

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Abstract. Glutathione S-transferase Pi (GSTP1) is an isozyme encoded by the GST pi gene that plays an important regulatory role in detoxification, anti-oxidative damage, and the occurrence of various diseases. The aim of the present study was to review the association between the expression of GSTP1 and the development and treatment of various cancers, and discuss GSTP1 methylation in several malignant tumors, such as prostate, breast and lung cancer, as well as hepatocellular carcinoma; to review the association between polymorphism of the GSTP1 gene and various diseases; and to review the effects of GSTP1 on electrophilic oxidative stress, cell signal transduction, and the regulation of carcinogenic factors. Collectively, GSTP1 plays a major role in the development of various diseases.

Correspondence to: Professor Lan Yi, Hengyang Medical College, Institute of Cytology and Genetics, Key Laboratory of Ecological Environment and Critical Human Diseases Prevention of Hunan Province Department of Education, University of South China, 28 Chang Sheng West Road, Hengyang, Hunan 421001, P.R. China
E-mail: yilanoky@126.com

Abbreviations: AML, acute myeloid leukemia; BaP, benzo(a) pyrene; BC, bladder cancer; CRC, colorectal cancer; ER, estrogen receptor; GST, glutathione-S transferase; GSTP1, glutathione S-transferase Pi; GSTM1, Mu-class glutathione S-transferase 1; GSTT1, glutathione S-transferase theta 1; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell carcinoma; iNOS, inducible NO synthase; JNK, c-Jun N-terminal kinase; Mn, manganese; MRP1, multidrug resistance protein 1; NF-κB, nuclear factor-κB; NSCLC, non-small cell lung cancer; NO, nitric oxide; PCa, prostate cancer; T2DM, type-2 diabetes mellitus

Key words: glutathione S-transferase Pi, expression, methylation, polymorphism, reactive oxygen species

Contents

1. GST family: Multifunctional enzymes involved in oxidative stress, poisoning, and cancer

The glutathione-S transferase (GST) family consists of a group of isoenzymes involved in phase II detoxification of xenobiotics by glutathione conjugation (1,2). It is widely found in nematodes, fruit flies, yeast, and the cytoplasm of higher vertebrates. Studies have shown that soluble GST accounts for 4% of total soluble protein in human and rodent livers (3). Three major protein subfamilies have been reported to exhibit glutathione transferase activity: Cytoplasmic, mitochondrial and microsomal GSTs (4,5). Microsomal GSTs are membrane-associated proteins in eicosanoid and glutathione metabolism (6,7). Cytoplasmic GSTs are the largest subfamily of these transferases and have unique activities. They catalyze the thiolysis of 4-nitrophenyl acetate, exhibit thiol transferase activity, reduce trinitroglycerin, dehydroascorbic acid and monomethyl decanoic acid, and catalyze ethyl maleate and 5-3 isomerization of ketosteroids (8).

According to the similarity in amino acid sequences, different structures of genes, and immunological cross-reactivity, GSTs are divided into seven subtypes (9) as follows: Alpha (α), pi (π), mu (μ), theta (θ), omega (ω), sigma (σ), and zeta (Table I). Among those, μ, θ and π are the most widely studied

GST subtypes in mammals (10). It is well known that μ-class glutathione S-transferase 1 (GSTM1) plays an important role in the toxicity and effectiveness of medical drugs. GSTM10 is the most common polymorphism, resulting in loss of enzymatic activity (11,12). Glutathione S-transferase θ 1 (GSTT1) plays a role in human carcinogenesis (13). GSTM1-null and GSTT1-null may contribute to the clinical course of patients with type 2 diabetes mellitus (T2DM) (14). GSTs interact with several factors, such as regulatory kinases, and modulate numerous pathways involved in cell proliferation, differentiation and death. Previous studies have demonstrated that GST plays a major role in cancer cell proliferation and death via its cytoprotective and regulatory functions (15,16). GST enzymes also play an important role in detoxifying chemotherapy drugs (17). They may be used to detoxify oxidized or alkylated drugs directly by combining active compounds or drugs (18). In addition to their well-characterized catalytic activity, there is evidence that GST isoenzymes also participate in regulating the expression of mitogen-activated protein kinases, and promote S-glutathionylation of cysteine residues in target proteins (19). In addition, genetic variants of GST have been reported to be involved in various fluorouracil- and platinum-based chemotherapies for the treatment of metastatic advanced cancers, such as acute myeloid leukemia (AML), gastrointestinal tumors, non-small cell lung cancer (NSCLC) and prostate cancer (PCa) (20,21). Therefore, it is clear that members of the GST family have a wide range of applications in detoxification and drug treatment.

2. GSTP1: A major regulator in the occurrence and development of cancer

GSTP1 is the most widely studied member of the GST family (22). The GSTP1 gene (π) is located on chromosome 11q13. It consists of nine exons and is 3.2 kb in length, protects cells from carcinogens and cytotoxins, and was originally isolated from a cosmid library. The gene spans ~3 kb and is interrupted by six introns with regions around the 5'-end having high G + C and CpG content typical of HpaII microfragment islands (23). In humans, GSTP1 usually consists of two identical dimeric subunits, each consisting of 210 amino acids and two binding sites, G and H. Different G and H sites with different amino acid residues in GST may play different roles. GSTP1 specifically binds to GSH or GSH analogs via the G site and catalyzes the interaction between GST amino acid residues and GSH thiols and conventional electrophiles at the H site (24). Therefore, G-site modification generally contributes to the development of specific GSTP1 inhibitors.

GSTP1 has a wide range of physiological functions: It is involved in metabolism, detoxification and elimination of potentially genotoxic foreign complexes, metabolizes a variety of carcinogenic compounds, and protects cells against DNA damage and canceration. In the GST family, early studies demonstrated that the GSTP1 gene plays an important role in several cellular processes, including catalysis and deoxylation of electrophilic compounds, oxidative stress regulation, cell signaling and carcinogenesis (25,26). GSTP1 actively protects cells from carcinogens and electrophilic compounds (27,28). It has been suggested that GSTP1 also protects cells from oxidants and electrophilic-mediated genomic damage (29). GSTP1 is involved in apoptosis resistance and metabolism of several chemotherapeutic agents. Platinum-based drugs have been found to be metabolized by GSTP1, allowing GSTP1 to be expressed in ovarian tumors. Therefore, GSTP1 may be used as a target gene and candidate response biomarker for platinum-based chemotherapy. In addition, GSTP1 plays a major role in the metabolism of cisplatin and carboplatin in ovarian cancer cells (30,31). Differences in expression of GSTP1 may affect the response of patients with ovarian cancer to platinum-based chemotherapy (32). Taken together, the studies on changes in GSTP1 expression of tumor cells may contribute to the development of antitumor drugs. GSTP1 appears hold promise in drug development, and the GSTP1 gene is involved in the regulation of activator proteins. It plays an important role in the regulation of tumor necrosis factor. Both activator protein 1 and nuclear factor (NF)-κB mediate regulation of GSTP through a redox process (33). A chimeric inhibitor that binds the affinity recognition moiety to a chelated transition metal has been explored to develop metal-mediated affinity reagents or drugs for hGSTP1-1 (34). GSTP1 is also a key regulator of hepatocyte proliferation during the initial stages of liver regeneration (35). The -323/-314 sequence located in the GSTP1 promoter binds to NF-κBp50/65 and p65/p65 dimers, and is involved in the regulation of this gene by tumor necrosis factor α (36-38). The GSTP1 gene (OMIM 134660) encoding the π-GST partial GSTP1-1 protein is widely expressed in most tissues, particularly in the lungs, esophagus and placenta (39). Ubiquitous epigenetic silencing of GSTP1 in PCa leads to increased survival and accumulation of potential priming DNA conjugates after exposure to long-term oxidative damage, suggesting that GSTP1 has protective and antitumor functions (40). As mentioned above, GSTP1 has important physiological functions in the detoxification and antioxidation of metabolites.

GSTP1 not only has important physiological functions, but also major pathological functions. GSTP1 is closely associated with exposure to low doses of ionizing radiation, heavy metals, and other chemicals (Table II). Manganese (Mn) has been shown to be a naturally occurring trace element that is essential for human health and development, but is neurotoxic at high concentrations (41,42). Studies have shown a possible synergistic effect between the blood Mn concentration and GSTP1 in autism spectrum disorder (43). GSTP1 is induced by lead and may be used as a biomarker for lead exposure. It is only involved in the changes during the later stages of lead poisoning (44,45). Previous studies have found that arsenic compounds are useful as drugs, but have toxic effects, and GSTP1 is a major factor in resistance to these drugs (46,47). GSTP1 detoxifies arsenic-based drugs by isolating the active site and dimer interface, reacting with cysteine in the presence of sufficient GSH under low GSH conditions (48,49). GSTP1 also reduces the retention time of As_2O_3 in the cells. Catabolism of H_2O_2 reduces the amount of H_2O_2 in the cells, thereby blocking apoptosis of lymphoma cells induced by As_2O_3 (50). In addition, GSTP1 may participate in the elimination of carcinogens in tobacco and participates in the occurrence of smoking-related lung adenocarcinoma. GSTP1 plays a role in the elimination of toxic substances from cigarette smoke in both normal lung and cancer cells (51). GSTP1 is also involved in the detoxification process of benzo(a)pyrene (BaP), which excretes the conjugates of BaP metabolism and

Table I. Classification of members of the GST family.

Class	Gene	Chromosome location	Gene size, kb	Protein size (AA)	Primary location	Refs.
Alpha	GSTA1		12.53		Liver, kidneys	(9)
	GSTA2		13.48		Liver	
	GSTA3	6p12.2	13.16	222	Adrenal	
	GSTA4		17.43		Adrenal, skin	
	GSTA5		14.44		Liver, kidneys	
Mu	GSTM1		21.14	218	Liver, ovary	(10,11)
	GSTM2		41.53	218	Ovary, skin	
	GSTM3	1p13.3	7.1	225	Testes, kidneys	
	GSTM4		18.76	218	Duodenum, intestine	
	GSTM5		63.66	218	Ovary, gallbladder	
Omega	GSTO	10q25.1	32.1	241	Liver, heart	(9)
Pi	GSTP1	11q13	3.06	210	Esophagus, thyroid	(9)
Theta	GSTT1	22q11.23	8.18	240	Gastric tissues	(13)
	GSTT2		3.88	244	Adrenal, skin	
Zeta	GSTZ1	14q24.3	10.71	216	Liver, testes	(9)
Kappa	GSTK1	7q34	26.76	226	Duodenum, small Intestine	(9)

GST, glutathione S-transferase.

Table II. Related mechanism of GSTP1 in pathological functions.

Exposure or irradiation	Related mechanism	Refs.
Heavy metals		
Manganese	Cooperate with blood Mn concentration in Autism Spectrum Disorder	(41,42)
Lead	Serves as a biomarker of lead exposure	(44,45)
Arsenic	Blocks arsenic trioxide-induced apoptosis in lymphoma cells	(46,47)
Ionizing radiation		
^{137}Cs	Stress response induced by low-dose irradiation in mouse liver	(55,56)
^{222}Rn	Protects cells from DNA damage	(53)
Other		
Smoking	Is involved in the occurrence of smoking-related lung adenocarcinoma	(51)
Tobacco	Participates in the elimination of carcinogens in tobacco	(51)
BaP	Involved in the detoxification process of BaP	(52)

BaP, benzo(a)pyrene.

detoxification (52). It is also involved in the protection of cells against ^{222}Rn-induced DNA damage (53). GSTP1 also blocks lipopolysaccharide (LPS) -induced overproduction of proinflammatory factors and has anti-inflammatory effects on the LPS response (54). Therefore, as a detoxifying enzyme, GSTP1 plays an important role in the detoxification of heavy metals and may facilitate exploring metal-mediated affinity drugs. GSTP1 is also closely associated with radiation damage. Our previous studies indicated that GSTP1 is involved in the radiation-induced stress response of liver tissue in C57BL/6J mice and it may be used as a biomarker of low-dose radiation for early identification of radiation contamination. Therefore, the mechanism of GSTP1 in the radiation-induced stress response is worthy of further investigation (55,56). Of note, the involvement of GSTP1 in the development of diseases is a complex process involving multiple steps and factors. GSTP1 is a key regulator in the occurrence and development of multiple cancer types.

3. Expression of GSTP1: A factor involved in the development of multiple cancer types

There is a close association between GSTP1 expression and tumor development. In several tumor tissues, >90% of active

Table III. Differences in the expression of GSTP1 are involved in the development of various types of cancer.

GSTP1 expression	Disease	Function	Refs.
Upregulation	Colorectal cancer	A clinically useful biomarker of colon cancer and a target for anti-colon cancer drugs	(8,60)
	Esophageal cancer	Reduces the chemosensitivity of cancer cells	(62,63)
	Thyroid cancer	Involved in carcinogenesis and growth of papillary thyroid cancer	(69)
	Breast cancer	Promotes autophagy resistance to ADR in breast cancer cells	(65)
	Non-small cell lung cancer	Inhibition of malignant growth and invasiveness of cisplatin-resistant NSCLC cells	(64)
	TCC	Contributes to increase in antioxidant capacity in TCC	(67,68)
	HCC	Inhibits the proliferation of HCC cells	(71)
	Malignant melanoma	Protects melanoma cells from toxic effects of etoposide	(72)
Downregulation	Prostate cancer	A useful biomarker for early detection and prognosis	(74)

TCC, transitional cell carcinoma; HCC, hepatocellular carcinoma; ADR, adriamycin.

GSTs is GSTP1 (57). Therefore, the difference in expression of GSTP1 in diseases such as tumors has attracted significant attention. Compared with normal tissues, the difference in GSTP1 expression is associated with multiple diseases (Table III). GSTP1 is highly expressed in various types of cancer and preneoplastic legions, such as colorectal, esophageal, lung, bladder, thyroid and breast cancer (58,59). GSTP1 is overexpressed at various stages of colorectal cancer, from abnormal crypt foci to advanced cancer (8,60). GSTP1 may be used as a clinically useful target for anti-colon cancer drugs (61). High expression of GSTP1 in esophageal cancer tissues may reduce the chemosensitivity of cancer cells (62,63). Increased expression of GSTP1 in bladder transitional cell carcinoma is associated with altered apoptotic pathways (64). Upregulation of GSTP1 expression contributes to an increase in the antioxidant capacity of bladder transitional cell carcinoma cells (65,66). High expression of GSTP1 plays a role in tumor growth and carcinogenesis of papillary thyroid cancer (67). Moreover, high expression of GSTP1 confers resistance of breast cancer cells to adriamycin by promoting autophagy (68). In addition, overexpression of GSTP1 inhibits the proliferation of HepG2 and Huh7 liver cancer (69). GSTP1 and multidrug resistance protein 1 (MRP1) are overexpressed in malignant melanoma. GSTP1 acts together with MRP1 to protect melanoma cells against the toxic effects of etoposide (70).

It is interesting that miRNAs regulate GSTP1, particularly in relation to human diseases. miR-133b overexpression contributes to the suppression of malignant growth and aggressiveness of cisplatin-resistant NSCLC cells by targeting GSTP1 (71). miRNA-130b may be involved in the development of drug resistance of ovarian cancer by regulating the expression level of the GSTP1 protein (72). Similarly, miR-133a directly regulates the GSTP1 gene in bladder cancer (BC) and mediates GSTP1-mediated anti-apoptotic effects by downregulation of miR-133a in human BC (73). There are also data suggesting that miR-133α in head and neck squamous cell carcinoma (HNSCC) regulates the carcinogenic effects of GSTP1, thereby providing new insights into the mechanisms underlying HNSCC carcinogenesis (74). Downregulation of GSTP1 may facilitate the function of miR-124 in doxorubicin resistance and enable the development of new treatments to overcome chemoresistance in colorectal cancer (CRC) patients (75). miR-513a-3p sensitizes human lung adenocarcinoma cells to cisplatin by regulating GSTP1 (76). Therefore, the regulation of GSTP1 by miRNA is crucial in several human diseases.

The expression of GSTP1 in tumors is low; for example, its expression in PCa is low, and downregulation of GSTP1 expression may play an important role in the progression of PCa (77). Downregulation of GSTP1 expression in PCa may be a useful biomarker for early detection and prognosis (78). Loss of GSTP1 expression in human PCa cells increases their susceptibility to oxidative stress-induced DNA damage and may be an important target for primary prevention of PCa (79). In certain diseases, the expression of GSTP1 may also play a regulatory and predictive role. GSTP1 expression may predict the pathological response to 5-fluorouracil/epirubicin/cyclophosphamide in estrogen receptor (ER)-negative tumors (80). The difference in the expression of GSTP1 is associated with multiple diseases and plays an important role in prediction and treatment.

4. GSTP1 methylation: A tissue biomarker that performs well in several types of malignancies

The promoter region of the GSTP1 gene is usually affected by methylation, and changes in methylation status suppress normal gene expression, which may lead to weakening or loss of its detoxification and antioxidant functions. In several cancer types, the GSTP1 gene is affected by hypermethylation. GSTP1 is a major tissue biomarker that performs well in several types of malignancies, such as PCa, breast and lung cancer, and hepatocellular carcinoma (HCC) (81). GSTP1 methylation has been found to be associated with the development of several diseases (Fig. 1). Recent research has confirmed that hypermethylation of GSTP1 inactivates the GSTP1 gene and plays a major role in liver cancer. It may

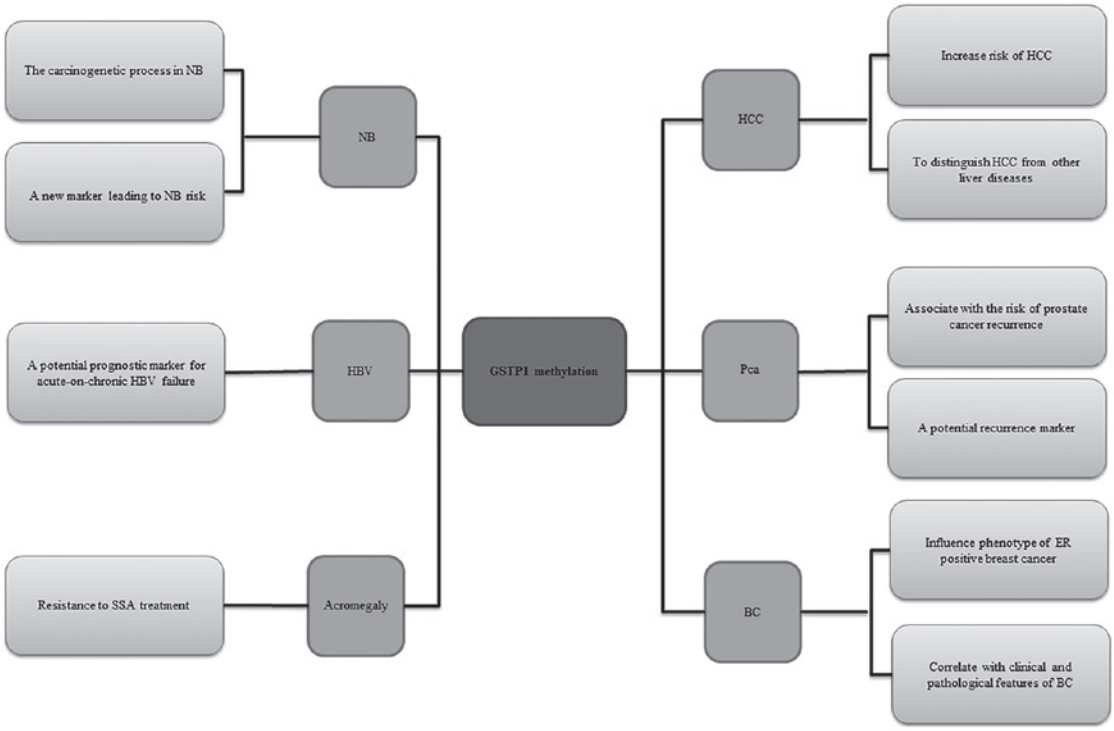

Figure 1. GSTP1 methylation is associated with the development of numerous diseases. GSTP1, glutathione S-transferase Pi.

increase the risk of HCC, and is also significantly associated with a poor prognosis of patients with HCC (82,83). It has been reported that hypermethylation of the GSTP1 gene promoter region may be a potential biomarker for distinguishing HCC from other liver diseases (84). Of note, methylation of the GSTP1 gene promoter may be associated with the invasiveness of HCC. Chronic hepatitis B virus infection may be responsible for inactivation of p16 induced by GSTP1 methylation (85). GSTP1 methylation is associated with oxidative stress-induced liver injury in acute-chronic hepatitis B liver failure. Abnormal methylation of the GSTP1 promoter is also present in acute-chronic hepatitis B liver failure and may have a high predictive value for short-term mortality. Therefore, GSTP1 may be a potential prognostic indicator of acute hepatitis B-related acute liver failure (86). GSTP1 methylation has a strong influence on liver-related diseases and may play a role in the treatment of liver-related diseases. GSTP1 methylation is associated with the recurrence and prognosis of PCa, and may be a potential epigenetic marker (87-92). Similar to PCa, GSTP1 hypermethylation also occurs in early events of breast cancer (93). The heterogenous DNA methylation pattern in the GSTP1 promoter is a major obstacle for DNA methylation analysis of the GSTP1 gene, which explains some of the contradictory differences in the role of GSTP1 promoter methylation in breast cancer (94). Although previous studies have shown no clear correlation between the GSTP1 status and the clinicopathological characteristics of PCa, GSTP1 methylation is associated with a more aggressive ER-positive breast cancer phenotype (95). Furthermore, GSTP1 methylation is associated with ER positivity (96-98). GSTP1 methylation was found to be correlated with the clinicopathological characteristics of breast cancer (99). Therefore, GSTP1 methylation is important for breast cancer research. The frequency of GSTP1 methylation in cancer tissues of patients with NSCLC ranges from 0 to 25%, while lower or no methylation is observed in adjacent benign tissues (100-105). Abnormal methylation of GSTP1 may contribute to the carcinogenesis of neuroblastoma and may be used as a new marker (106). In addition, in acromegaly, methylation of the GSTP1 gene is associated with resistance to treatment with somatostatin analogues (107). Therefore, GSTP1 methylation appears to play a key role in numerous diseases.

5. GSTP1 polymorphism: A potential biomarker for cancer risk

It has been demonstrated that GSTP1 enzymatic activity is strongly dependent on a single-nucleotide polymorphism, the A313 G polymorphism, which replaces isoleucine (Ile) with valine (Val) at the 105 amino acid position (Ile105Val) (IE), producing three GSTP1 genotypes: Ile/Ile homozygous wildtype, Ile/Val heterozygotes, and Val/Val homozygous variants (108,109). Genetic polymorphism of GSTP1 is associated with several cancer types. The genetic polymorphism of GSTP1 may be associated with the detoxification of polycyclic aromatic hydrocarbons in cigarette smoke and exhibits the highest expression in lung tissue (110,111). In the Chinese population, the GSTP1 Ile105Val polymorphism may increase the risk of lung cancer (112-114). Furthermore, GSTP1 exon 5 polymorphism is associated with lung cancer susceptibility. Stratified analysis has revealed a correlation between the GSTP1 exon 5 gene polymorphism and the risk of lung squamous cell carcinoma (115). GSTP1 genotyping may help identify patients at higher risk of developing anti-tuberculosis treatment-related hepatotoxicity (114,116). GSTP1 gene polymorphism may also be used as an independent prognostic

Table IV. Related mechanism of action of GSTP1 gene polymorphism in various diseases.

Tissue/Cell	GSTP1 polymorphism	Disease	Related mechanism	Refs.
Cancer or tumor	GSTP1 exon 5 polymorphism	Lung cancer	Increased lung cancer susceptibility	(111)
	GSTP1 Ile105Val	Colorectal cancer	Increased risk of colorectal cancer	(114,115)
	GSTP1 Ile105Val	Skin cancer	Genetic contribution to the development of skin cancer	(116,117)
	GSTP1*B GSTP1*C	Prostate cancer	Biomarker of prostate cancer risk	(116,118)
	GSTP1 Ile105Val	Gastric cancer	Reduces the risk for premalignant lesions	(119,120)
	GSTP1: rs4147581 genotypes	Hepatocellular carcinoma	Independent prognostic marker for HCC patients	(114)
	GSTP1 rs1695 GG genotype	Osteosarcoma	Affects prognosis of osteosarcoma patients receiving chemotherapy	(124,125)
	GSTP1 Val/Val genotype	Oral squamous cell carcinoma	Affects the risk of developing oral squamous cell carcinoma	(128)
	GSTP1 gene I105V	Leukemia	Affects the risk of developing leukemia	(130)
Other diseases	GSTP1 Ile105Val	Type 2 diabetes mellitus	Affects the risk of developing type 2 diabetes mellitus	(136,137)
	GSTP1 A114V	Motor neuron disease	Affects the risk of motor neuron disease	(140)
	GSTP1 A114V	Chronic kidney disease	Affects the incidence of chronic kidney disease	(141,142)

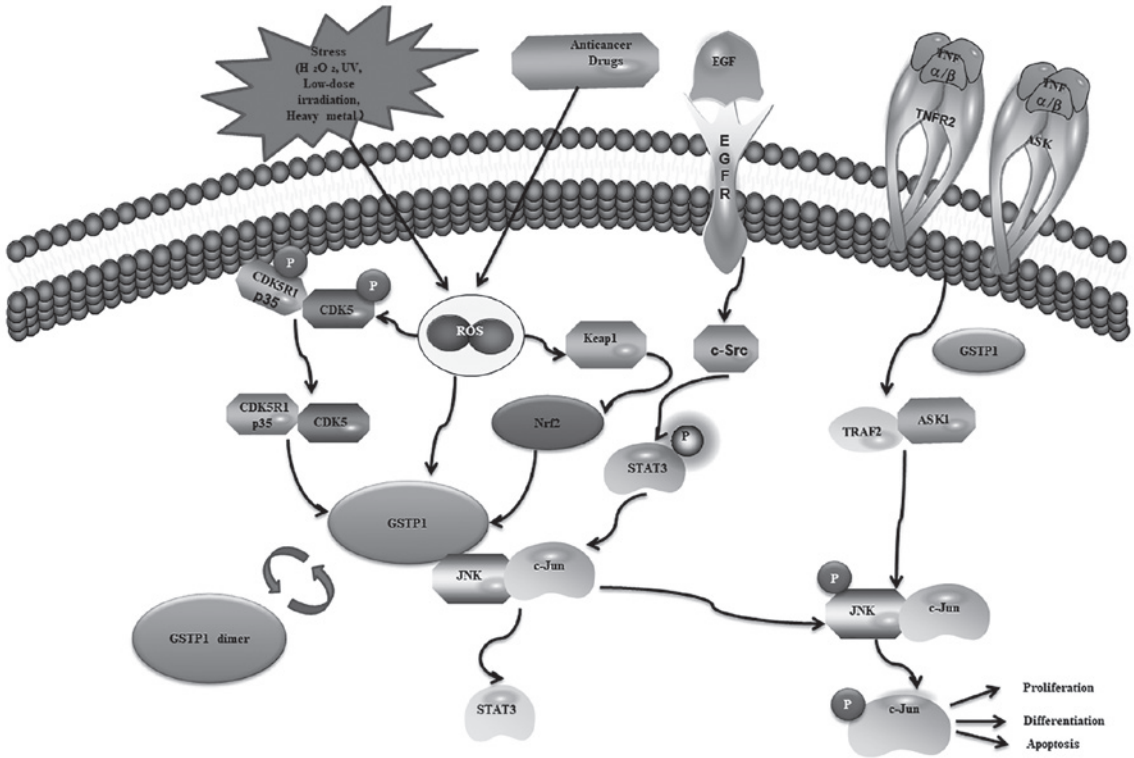

Figure 2. GSTP1 is involved in endogenous regulation of cellular signaling pathways. GSTP1, glutathione S-transferase Pi.

marker for patients with HCC (117). GSTP1 Ile105Val may be associated with an increased risk of CRC (118,116). The Ile105Val polymorphism of the GSTP1 gene may also have a genetic effect on the occurrence of skin cancer (119,120). The GSTP1 polymorphism has been shown to be a potential biomarker for PCa risk (121,122). The GSTP1 Ile105Val polymorphism may also be associated with the risk of gastric cancer (123,124), and the GSTP1 Val allele appears to reduce

the risk of premalignant lesions (125,126). An interesting finding is that the GSTP1 *C variant may exert protective effects against pancreatic cancer in the elderly (127). It has been demonstrated that GSTP1 is associated with response to chemotherapy, PFS and OS in patients with osteosarcoma, and GSTP1 polymorphism may help design individualized treatments (128,129). GSTP1 gene polymorphism may also play an important role in the prognosis of osteosarcoma patients treated with chemotherapy (130,131). In addition, GSTP1 gene polymorphism is associated with risk of oral SCC (132). The GSTP1 codon 105 polymorphism may play a major role in leukemia by altering the protein function and reducing its ability to detoxify certain mutagens and carcinogens, which may result in increased DNA damage and mutations that increase cancer risk (133). An individual with at least one Val allele at codon 105 of the GSTP1 enzyme may be susceptible to cancer. Following cytotoxic chemotherapy, the Val allele at GSTP1 codon 105 may result in treatment-related AML (134). It has been reported that GSTP1 polymorphism is important for the development of AML and the formation of AML-specific chromosomal abnormalities (135,136). Variant genotypes of the GSTP1 Ile105Val gene polymorphism may contribute to the risk of chronic myelogenous leukemia (137-139). Therefore, GSTP1 gene polymorphism may contribute to the treatment of leukemia.

GSTP1 gene polymorphism is not only involved in the development of cancer, but is also associated with a number of other diseases (Table IV). Diabetic neuropathy is a common complication of T2DM, and GSTP1 gene polymorphism may contribute to the development of T2DM (140,141). There is no clinical proof that GSTP1 IIe105Val polymorphisms affect the risk of gestational diabetes mellitus in a Chinese population (142). A significant correlation has been found between the GSTP1 (105) Ile/(105)Ile genotype and the development of grade ≥2 docetaxel (taxotere)-induced peripheral neuropathy (143). It has been demonstrated that the presence of the GSTP1 A114V rather than the I105V variant increases the risk of motor neuron disease (MND). Moreover, the combination of GSTP1 polymorphisms in codons 105 and 114 may result in protective reduction in the toxicity of electrophilic compounds to organic and inorganic hydrogen peroxides in MND patients (144). GSTP1 polymorphism plays a role in the incidence of chronic kidney disease and is associated with higher numbers of micronuclei (145,146). The GSTP1 Ile105Val genotype may affect the excretion and metabolism of inorganic arsenic (147). Furthermore, changes in GSTP1 may affect the risk of non-photo-induced drug eruptions (148). It has been found that the GSTP1 Ile105Val polymorphism is also associated with inter-individual variations in urinary and blood arsenic levels (132). Thus, GSTP1 gene polymorphism is closely associated with various diseases and may prove to be helpful for the development of therapeutic drugs.

6. GSTP1: A key factor involved in complex processes mediated by multiple signals

GSTP1 may mediate the storage and transport mechanisms of gases and react with some compounds. Nitric oxide (NO) plays an important role in cell signaling, blood pressure, coagulation, and tumor cell killing. A novel GSTP1 and multidrug resistance protein 1-mediated NO storage and transport mechanism (MRP1/ABCC1) protects an M1-macrophage model from the effect of NO (149-153). GSTP1 also reduces the inducible NO synthase (iNOS) protein level. GSTP1 regulates iNOS by affecting S-nitrosylation, dimerization and stability (154). It is also associated with some chemicals in the human body, and 1-octyl-3-methylimidazolium bromide upregulates GSTP1 (155). The compound 4b ('p-cyano-PABA/NO') is more favorable for product distribution in the presence of GSTP1 (156). GSTP1 is also involved in endogenous regulation of cellular signaling pathways (Fig. 2). The c-Jun N-terminal kinase (JNK)-mediated cell signaling pathway is endogenously regulated by protein-protein interactions with GSTP1 (157). It is believed that there is a direct interaction between the C-terminus of JNK and GSTP1, and GSTP1 is considered to act as a key ligand-binding protein that regulates the kinase pathway (158). GSTP1 binds to mitogen-activated protein kinase JNK and inhibits JNK downstream signaling (159). Epidermal growth factor receptor phosphorylation of GSTP1 enhances JNK signaling and provides a survival advantage for tumors (160). GSTP1 acts as a direct inhibitor of JNK *in vivo* to regulate constitutive expression of specific downstream molecular targets of the JNK signaling pathway (161). The mechanism of GSTP1 protection against serum depletion-induced cell death is mediated through an apoptosis signal-regulating kinase 1 (ASK1) pathway, ASK1-MKK7-JNK (162). There may also be a novel non-enzymatic effect of GSTP, which plays an important role in the regulation of the classical ERα signaling pathway by modification of transcriptional cofactors, such as receptor interacting protein 140 (163). Increased levels of GSTP1 may be another mechanism regulating cyclin-dependent kinase-5 signaling, eliminating oxidative stress, and preventing neurodegeneration (164). Transcriptional activation of the GSTP1 gene is also regulated by the Nrf2 pathway (165). GSTP1 plays an important role in the regulation of signal transduction. Therefore, GSTP1 may be involved in complex processes mediated by multiple factors and multiple signals.

7. Conclusion

As an important phase II detoxification enzyme, GSTP1 is involved in the development and progression of various types of cancer. The expression, methylation and genetic polymorphisms of GSTP1 are closely associated with cancer. GSTP1 plays an important regulatory role in the metabolism, detoxification and elimination of potentially genotoxic foreign complexes. Therefore, GSTP1 may act as a critical regulator in the occurrence and development of multiple cancer types.

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Authors' contributions

JC made substantial contributions to conception and design of the study, acquisition, analysis and interpretation of data, revised the manuscript critically for important intellectual content, and was a major contributor to writing the manuscript. GL, JY, LL, YT, HW, BL, LD, JT and YC were involved in drafting the manuscript. LY made substantial contributions to the conception and design of the study, acquisition, analysis and interpretation of data, and gave final approval of the version to be published.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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