


GSTM3 Function and Polymorphism in Cancer: Emerging but Promising

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Abstract: Cancer is a major cause of human mortality; however, the molecular mechanisms and proteomic biomarkers that cause tumor progression in malignant tumors are either unknown or only partially revealed. Glutathione S-transferases mu3 (GSTM3), which belongs to a family of xenobiotic detoxifying phase II enzymes, is associated with carcinogen detoxification and the metabolism of exogenous electrophilic substances. It has been reported that GSTM3 has different polymorphisms in various tumor cells and regulates tumorigenesis, cell invasion, metastasis, chemoresistance, and oxidative stress. Deep research into the regulatory mechanisms involved in disorders of GSTM3 expression and the function of GSTM3 in different cancers may facilitate improvements in cancer prevention and targeted therapy. The combination of GSTM3 with other family members can regulate the carcinogenesis and susceptibility to different cancers in humans. GSTM3 also regulates the reactive oxygen species (ROS) and participates in oxidative stress-mediated pathology. Here, we provide a general introduction to GSTM3 in order to better understand the role of GSTM3 in cancer.

Keywords: GSTM3, cancer, polymorphism, ROS

Introduction

Cancer remains a critical cause of human mortality. It is reported that globally there will be approximately 22 million new malignant tumor diagnoses and 13 million mortalities each year by the 2030s.¹ Carcinogenesis maybe caused by variants in genetic levels, and in turn, genetic factors can influence the incidence rate. Glutathione S-transferases (GSTs) include a family of xenobiotic detoxifying phase II enzymes which mainly catalyze the connection of glutathione to a variety of electrophilic chemical compounds, which are involved in carcinogen detoxification and the metabolism of various bioactive compounds.² GST families are highly polymorphic, and allele mutations or genetic deletions of a certain base lead to a predisposition for development of human cancer.³ Eight different classes of these cytoplasmic mammalian GSTs have already been identified: mu, pi, alpha, omega, kappa, sigma, zeta, and theta. The most widely studied families are mu (GSTM), pi (GSTP), alpha (GSTA), and theta (GSTT).⁴

The genes which encode GST mu3 are located on chromosome 1p13.3 and are known to be highly polymorphic.⁵ At present, GST mu3 is known to have two alleles: GSTM3*A and GSTM3*B. Like the GST family, the *GSTM3* gene exerts an important function in the detoxification of the chemical substrates or electronic compounds, such as toxins, carcinogens, and production of oxidative stress.^{6,7} The relationship

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between the GST family and cancer has been widely explored, but the exact role of the *GSTM3* gene has not been fully elucidated. The *GSTM3* gene has been shown to significantly regulate individual susceptibility to cancers, such as laryngeal cancer, urinary cancer, and breast cancer.^{8–11} Contradictory conclusions have been published previously regarding the connection between polymorphic *GSTM3* and protective or risky results in different malignant neoplasms. This is the first review of *GSTM3* and it aims to provide a comprehensive overview of the functional expression and polymorphism of the *GSTM3* gene in oral and esophageal carcinomas, prostate carcinoma, renal cancer, lung cancer, and other cancers. Additionally, it aims to briefly describe the molecular mechanisms involved in the progression of malignant disease.

GSTM3 Gene Function

It has been confirmed that the *GSTM3* gene exerts an important role in the metabolism of toxic agents, such as the polyaromatic hydrocarbon, benzo (a) pyrene, that is released from tobacco. *GSTM3* has overlapping substrate specificity with *GSTM1*.² Each GST gene from each class is totally clustered on the identical chromosome.⁴ The *GSTM1*–*GSTM5* genes are located on chromosome 1p and occupy a length of approximately 100 kb. The genes which encode

the mu class 3 of GST are reported to be localized on 1p chromosome 13.3. The most common subtype is *GSTM3**A. On the other hand, *GSTM3**B has a 3-base pair deletion in intron 6, which produces a recognition binding site for yin yang 1 (YY1), regarded as the transcription factor assumed to regulate the *GSTM3* expression (Figure.1). YY1, a zinc finger transcription factor, can either activate or repress transcription with different efficiencies in the metabolism of carcinogens.¹² *GSTM3* also shares an amino acid sequence identity of about 70% with members of the mu class and less than 35% sequence identity with the alpha, pi, and theta classes, indicating that the *GSTM3* enzyme functions in the detoxification of carcinogenic compounds.¹³ Moreover, it shows a linkage disequilibrium with the *GSTM1* genotype.⁵ It can change the three-dimensional structure and make this region more susceptible to DNA-conjugated proteins, thus affecting the genetic regulation of other *GSTM* genes. Studies have indicated that changes in the expression level of *GSTM3* have been observed in renal cancer, colon cancer, breast cancer, cervical cancer, and other cancers.^{14–18} Moreover, except for various neoplasms, *GSTM3* is also reported to exert an important function in other kinds of diseases, such as Alzheimer's disease, cataracts, neurocysticercosis, cystic fibrosis, and Brugada syndrome.^{19–24}

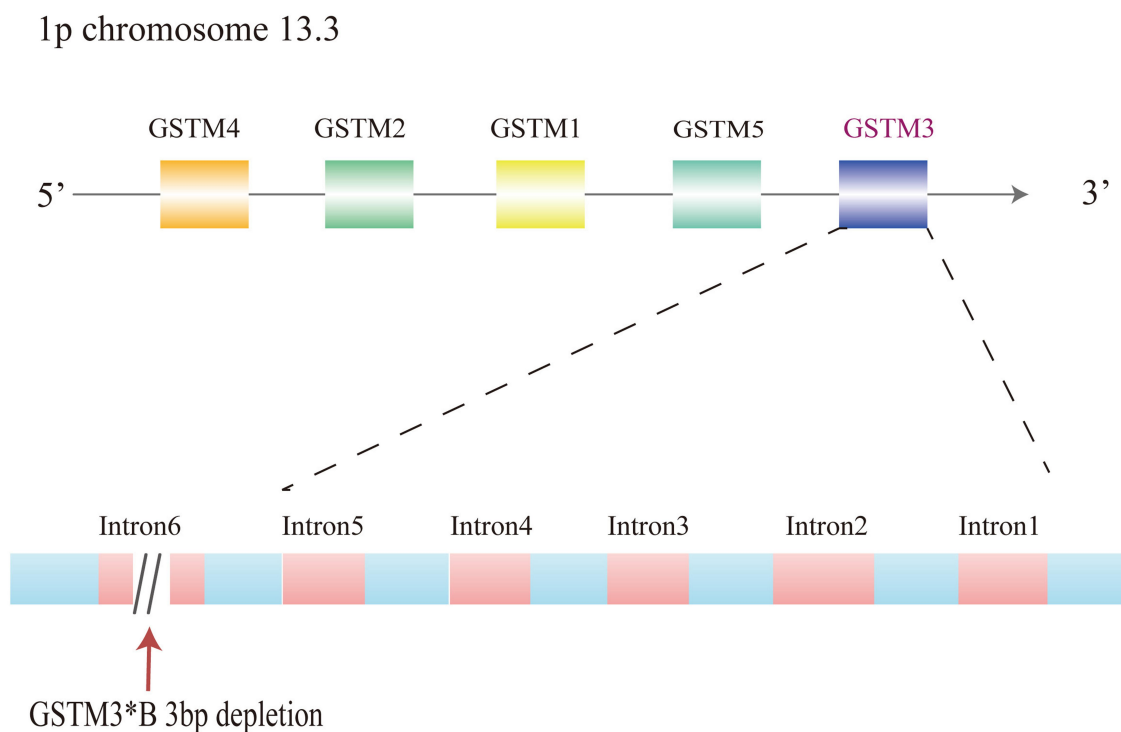


Figure 1 Gene cluster of *GSTM1*–*5* arranged as 5'–*GSTM4*–*M2*–*M1*–*M5*–*M3*–3' and mutations of *GSTM3* on chromosome 1p13. 3.

In addition, *GSTM3* presents an ethnic polymorphism frequency. The homozygous wild type (*GSTM3**A) is more common than the homozygous type (*GSTM3**B).²⁵ In a Caucasian population from the United Kingdom, the frequency of *GSTM3* polymorphism was 71% for the homozygous wild type (*GSTM3**A) and only 4% for the homozygous type (*GSTM3**B).⁵ Furthermore, such frequencies were also shown in people from Italy, Romania, and Sweden.²⁵ However, in Asian countries, the polymorphic rate of wild type (*GSTM3**A) was up to nearly 8289% in India and Malaysia.^{26,27} Moreover, the *GSTM3**B genotype was more frequently observed in Africans compared to Europeans.^{28,29} Besides, the polymorphism of *GSTM3* has also been reported to act as a hazard element for malignant tumors, but with conflicting consequences in different races, which might be aroused by a homozygous deletion of the *GSTM3* gene.^{30,31}

The Role of *GSTM3* in Cancers

Cancers in the Urinary System

GSTM3 has been reported as being dysregulated in various cancers and the protein expression of *GSTM3* has been reported to exert a peculiar function in the progression or inhibition of tumors (Figure 2). In renal clear cell carcinoma

(RCC), Wang³² showed that *GSTM3* rs1055259 was significantly associated with susceptibility to RCC. It was also verified to modify the *GSTM3* protein synthesis by blocking miR-556 binding, then reducing the activity of reactive oxygen species (ROS) and the progression of RCC. Furthermore, Tan¹⁵ found that the upregulation of *GSTM3* decreased the ability of anchorage-independent growth in renal cancer cells, which clearly proved that *GSTM3* serves as a tumor suppressor in RCC. Furthermore, a case-control study showed that the C allele of *GSTM3*-rs1332018 predicted poor prognosis. The immunohistochemistry revealed different *GSTM3* expression patterns in nephrons. In addition, global analysis of gene expression in RCC specimens also showed that *GSTM3* varied in different parts of the tissue.³³

Cancers in the Reproductive System

As for prostate cancer (PC), a bioinformatics analysis using the Gene Expression Omnibus database showed that the dysregulation between hsa-let-7a-5p/*CDKN1A* and hsa-miR-92b-3p/*GSTM3* pairs was associated with platinum-based chemoresistance of metastatic PC.³⁴ The *GSTM3* rs7483 polymorphism may be a promising biomarker for prostate cancer patients treated with androgen-deprivation therapy.³⁵ In metastatic PC, *GSTM3* rs7483

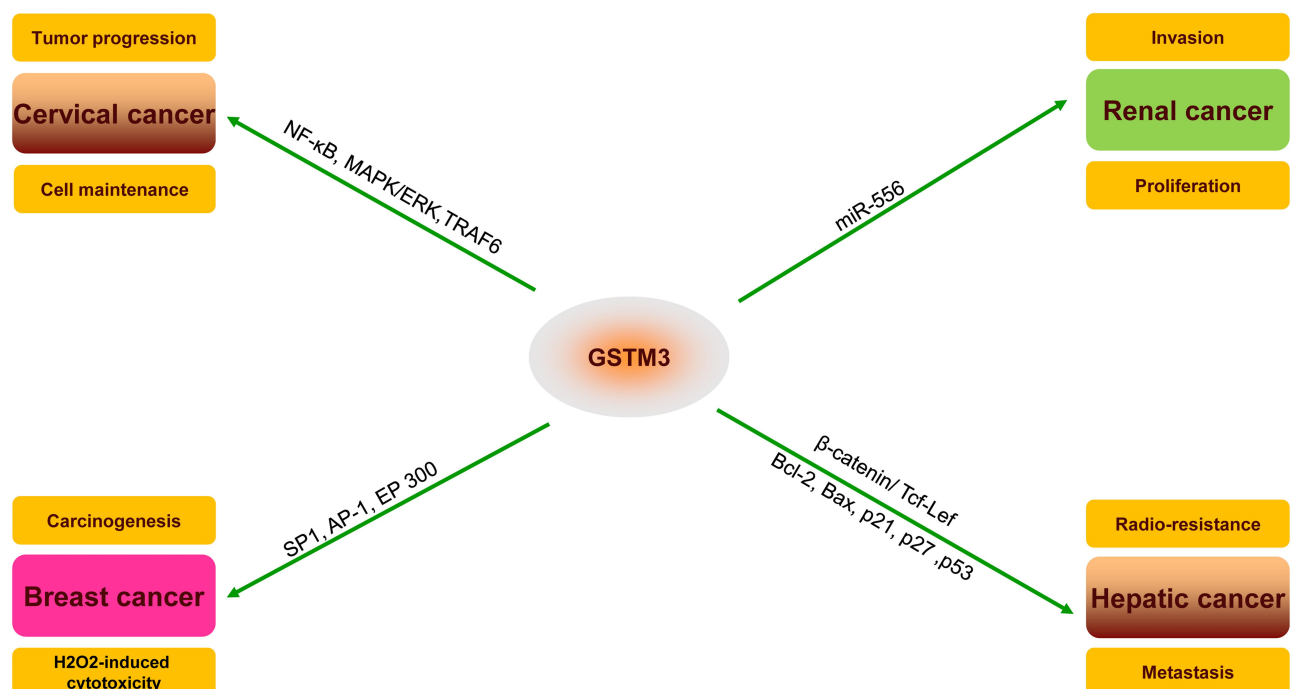


Figure 2 Important substrates and pathways for the potential mechanism and regulation of *GSTM3* in different cancers (TNF receptor-associated factor 6, TRAF6; mitogen-activated protein kinase, MAPK; extracellular regulated MAP kinase, ERK; nuclear factor kappa B, NF-Kb; Sp1 transcription factor, SP1; AP-1 transcription factor, AP-1; E1A binding protein p300, EP300; T-cell factor/lymphoid enhancer-binding factor (TCF/LEF); BCL2 apoptosis regulator, BCL2; BCL2-associated X, apoptosis regulator, BAX).

was associated with significant risk of progression. In non-metastatic PC, the AG/GG allele in GSTM3 rs7483 was associated with a lower risk of progression to castration-resistant prostate cancer. In terms of cervical cancer, Alberto¹⁶ pointed out that GSTM3 influenced cell maintenance, cell apoptosis, and the intracellular stress response through the NF- κ B and MAPK/ERK signal pathway. In HeLa cells, GSTM3 interaction with TRAF6 was predicted by the SysBiomics databases,³⁶ then identified by co-immunoprecipitation. Recently, Lollo also pointed out that GSTM3 acted as a key epithelial–mesenchymal transition inducer operating in amniotic epithelial cells using RNA sequencing.³⁷

Cancers in the Digestive System

As for hepatoma, GSTM3 plays a vital role in reversing the radio-resistance of hepatic cell carcinoma (HCC). It could also be an effective therapeutic target because it makes HCC cells sensitive to radiotherapy. GSTM3 also regulates the expression of Bcl-2, Bax, p21, p27, and p53, which are related to the cell cycle and cell apoptosis.³⁸ The level of GSTM3 mRNA expression in HCC cells showed a significant connection with the process of cellular detoxification, which also prompts the metastatic ability in cancer cells. GSTM3 might be a new downstream gene of the β -catenin/Tcf-Lef pathway in hepatic cancer cells.³⁹ Hepatitis is also known to correlate with hepatic cancer. Qi⁴⁰ reported that the methylation of GSTM3 promoter was associated with oxidative stress-related liver failure. Furthermore, it could also influence the severity of liver damage in patients with acute-on-chronic hepatitis B. Then, Sun⁴¹ found that the low methylation level of GSTM3 promoter predicted good prognosis of hepatitis B liver failure. In colon cancer, Stephan¹⁴ used tissue-based proteomics to show a strong association between gene expression level and metastatic lymph nodes. The over-expression of GSTM3 reduced the overall survival rate of patients.¹⁸ As for chemotherapy, metastatic colon cancer cells treated with cisplatin demonstrated an increasing level of GSTM3 expression than cells without cisplatin treatment.⁴²

Other Cancers

Currently, the exact function of GSTM3 in breast cancer is still unclear. It has been reported that the mRNA expression level is high in HER2-positive or ER-positive cancer types. Estrogen could stimulate ER to recruit the SP1, AP-1, and EP 300 transcription factors to bind to the GSTM3

promoter, resulting in upregulation of the GSTM3 gene in ER-positive breast cancer.^{43,44} On the other hand, ER α -mediated GSTM3 downregulation could prevent the H₂O₂-induced cytotoxicity and enhance the carcinogenic process of breast cancer. Long-term tamoxifen treatment for breast carcinoma has been reported to reduce levels of GSTM3 and enhance the sensitivity to H₂O₂.⁴⁴ Besides, Asik found that GSTM3, together with another phase II enzyme GSTZ1, were increased under the high concentrations of 2-amino-2-deoxy-glucose treatment in breast cancer cells.⁴⁵ Besides, when it comes to glioma, Li⁴⁶ showed that GSTM3 had a structure to integrate with long LncRNA growth-arrest specific transcript 5 and downregulated GSTM3, inhibiting the proliferation, invasion, and migration, but exerting apoptosis and enhancing oxidative stress.

GSTM3 Gene Polymorphism in Cancer

Single-nucleotide polymorphisms (SNPs) of the cancer-encoding gene have been identified to alter the genetic expression and influence the morbidity of cancers in different individuals. Genotyping of the important alleles for the gene has been associated with cancer risk, and there is a strong linkage between a kind of polymorphism and increasing progression of certain cancers. Several studies have indicated that the SNPs of GSTM3 could change the activity of enzymes, which modify the effect on personal sensitivity to toxins or pathologies.⁴⁷ Indeed, there are plenty of studies that have affirmed that the polymorphisms of GSTM3 are strongly associated with carcinogenesis and tumor progression^{15,29,32} (Table 1).

HNC Cancer

Head and neck cancer (HNC)—including cancers of the oral cavity, pharynx, and larynx—is the sixth most common malignant tumor globally.⁴⁸ Cha⁴⁹ demonstrated that the overexpression of the GSTM3*B allele seemed to be associated with an increased risk of laryngeal squamous carcinoma. Nadejda⁵⁰ collected peripheral blood samples from 129 patients and 172 healthy controls. Then, he verified the linkage between the cancer risk and the polymorphisms of GSTM3. The results showed that patients with the GSTM3 (AB or BB) genotype had a two-fold risk of larynx cancer than healthy individuals. However, Matthias⁵¹ found a reduced frequency of GSTM3 (AB or BB) alleles in larynx cancer patients compared to healthy

Table I General List of the GSTM3 Polymorphism and Cancer Risk in Different Types of Malignant Tumors

Cancer Type	Author	Year	Numbers	Genotype/ rs	Conclusion	Ref.
Laryngeal carcinoma	Matthias	1998	398	F	There is no significant difference between patients and healthy individuals	[51]
	Nadejda	1999	301	(AB or BB)	There is strong association between GSTM3 and laryngeal cancer	[50]
	Cha	2010	190	-	A significant relationship exists between GSTM3 and laryngeal cancer	[49]
Esophageal cancer	Jane	2007	349	(AB)	GSTM3 polymorphism influences the risk for histology and tumor region	[8]
Oral cancer	Nilabja	2004	256	(A)	GSTM3 genotype serves as a marker from leukoplakia to oral cancer	[52]
	Mousumi	2005	507	(A)	GSTM3 enhances the progression from leukoplasia to cancer	[53]
	Rao	2017	45	F	There is no difference between patients and control individuals	[54]
Lung cancer	Sisko	1995	100	-	Pulmonary expression of GSTM3 has association with lung cancer	[56]
	To-Figueras	2000	176	(AA)	GSTM3 increases lung cancer susceptibility	[59]
	Risch	2001	389	-	The risk alleles for GSTM3 conferring reduced enzyme activity were high	[57]
	Sissung	2019	103	rs7483	GSTM3-rs7483 were associated with paclitaxel progression-free survival	[61]
Prostate cancer	Medeiros	2004	150	-	GSTM3 may be an important biomarker for the risk of prostate cancer	[63]
	Pravin	2009	304	(AB + BB)	GSTM3 is associated with cancer risk in cigarette and alcohol consumers	[62]
Bladder cancer Renal cancer	Schnakenberg	2000	146	(B)	GSTM3 is significantly protected against the bladder cancer	[9]
	Tan	2013	400	rs1332018	GSTM3-rs1332018 genetic variants predict an unfavorable prognosis	[15]
	Wang	2018	329	rs1055259	A polymorphism GSTM3-rs1055259 reduces susceptibility of renal cancer	[32]
Cervical cancer Breast cancer	Hariom	2008	318	(AB)	GSTM3*AB genotypes increase the risk of cervical cancers	[65]
	Yu	2010	1632	rs4970737	SNP of the GSTM3 contributes to the carcinogenesis of breast cancer	[66]
	Jaramillo	2015	361	F	GSTM3 has no association between genes and breast cancer susceptibility	[67]
Colorectal carcinoma	Loktionov	2001	561	(B)	The polymorphic genotypes of the GSTM3 influence the individual risk	[68]
	Cortessis	2001	974	F	GSTM3 has no correlation with the risk of colorectal adenomas	[69]
Glioma	Roos	2006	498	(B)	The GSTM3 *B genotype was associated with increased risk of glioma	[72]
	Judith	2007	2337	F	No association between GSTM3 polymorphisms and adult brain tumor risk	[72]
Basal cell carcinoma	Yengi	1996	586	-	GSTM3 polymorphism serves as risk factors	[64]

Notes: F: no significant relationship; -: not mention

people. As for esophageal cancer, Jain⁸ reported that patients with the heterozygous genotype GSTM3*AB had an increased risk of esophageal cancer. Moreover, GSTM3 polymorphism might modulate the risk of adenocarcinoma and the region of the tumors. Besides, Nilabja⁵² reported that smokers with the GSTM3*A genotype were at higher risk of oral cancer than controls. Furthermore, in 2005, Mousumi substantiated the study by Nilabja with expanded sample sizes. The genotype GSTM3*A increased the susceptibility of oral cancer among smokers.⁵³ However, Rao failed to observe a relationship between GSTM3 polymorphism and risk of developing oral carcinoma.⁵⁴ A meta-analysis by Xu drew the conclusion that the GSTM3*A/B could act as a crucial protective genotype for HNC, especially for laryngeal cancer.⁵⁵

Lung Cancer

GSTM3 has been reported to express inconsistently in lung tissue, and this gene has the ability to increase the susceptibility to lung cancer.^{56–58} Sisko⁵⁶ showed that overexpression of this gene might lead to development of adenocarcinoma in the lungs of GSTM1 null individuals. However, GSTM3 was not influenced by the GSTM1 genotype in long-term smokers. In addition, Figueras⁵⁹ noticed that the combined genotype between GSTM1 null and GSTM3*AA might increase the lung cancer risk. Moreover, Risch⁵⁷ showed that the risky allele for GSTM3 conferring reduced enzyme activity was present at high levels in squamous cell carcinomas. This result was in accordance with a decreased detoxication of carcinogenic substances from cigarette smoke that tends to lead to development of squamous cell carcinomas. On the contrary, the meta-analysis performed by Feng in 2012 showed little connection between GSTM3 polymorphism and the risk of lung cancer.⁶⁰ Sissung showed that GSTM3 rs7483 was associated with paclitaxel progression-free survival in lung cancer patients.⁶¹ Therefore, the correlation between GSTM3 polymorphism and the risk of lung cancer still needs to be explored.

Prostate Cancer

The mutation of the GSTM3 gene has also been shown to enhance the risk of cancer formation in the urogenital system, particularly the susceptibility to prostate carcinogenesis. Pravin analyzed the GSTM3 intron 6 polymorphisms among Indian patients with PC and pointed out that the GSTM3 (AB + BB) genotype took part in the evolution of PC.⁶² And the risk was increased in cigarette

smokers and alcohol consumers. Another study from Medeiros showed the function of different alleles of GSTM3 in PC patients in Europe, and the polymorphism in the GSTM3 might be an important biomarker for PC risk.⁶³ Moreover, GSTT1 null was reported to be over-represented in advanced PC patients. The carriers of the GSTM3*BB genotype are reported to have a five-fold increased risk of PC. GSTM3*B, regarded as an at-risk allele, increases the transcriptional potentiality, and strengthens the detoxication ability of GSTM3-encoding protein.⁶⁴ The above evidence could demonstrate that carriers of GSTM3 variant genotype apparently played an important function in mediating susceptibility for PC. Larger-scale molecular investigations are needed to verify the role of GSTM3 genetic polymorphisms in PC.

Other Cancers

GSTM3 has also been investigated in other malignant tumors because of its polymorphism. As for bladder cancer, Schnakenberg⁹ proved that the intron 6 mutation of GSTM3 enhanced the susceptibility to bladder carcinoma. And Hariom⁶⁵ showed that GSTM3*AB genotypes might increase the risk of cervical cancers. Moreover, Yu⁶⁶ pointed out that SNP of the GSTM3 gene cluster could contribute to the carcinogenesis of breast cancer. And the catalyzing ability of GSTM3 in normal tissue could act as a protective factor against the risk of breast carcinoma. However, Jaramillo-Rangel⁶⁷ proved that GSTM3 has no association with breast cancer susceptibility. In colorectal carcinoma, the interactions of polymorphic genotypes of GSTM3 influenced individual risk and the absence of the GSTM3*B variant was a protective factor, especially its association with the GSTM1 genotype.⁶⁸ However, another case-control study by Cortessis reported that GSTM3 had no correlation with the risk of colorectal adenomas.⁶⁹ One meta-analysis concluded that the polymorphisms in GSTM3 (AA versus BB) and osteosarcoma risk were significantly correlated.⁷⁰ An observational study in North America demonstrated that GSTM3 also contributed to increased susceptibility to meningioma and glioma,⁷¹ but the same conclusion was not verified in residents of Europe.⁷² Besides, Yengi also showed that GSTM3 polymorphism interactions with cytochrome P450 served as risk factors for multiple cutaneous basal cell carcinoma.⁶⁴ Taken together, no one can ignore the association between GSTM3 polymorphism and tumorigenesis. The exact role of GSTM3 polymorphism and its

underlying mechanisms in the suppressibility of cancer still need to be explored in larger studies.

GSTM3 Interaction with Other GSTs in Carcinogenesis

The correlation of different genotypes among the GST gene family influences the individual risk of tumorigenesis. Besides GSTM3, many researchers have paid attention to the interaction between genetic variants in other GSTM family genes. The co-function of GSTM1 and GSTM3 has been widely investigated. Genetic variants in the GSTM3 gene depend on GSTM1. Some studies have also pointed out that the GSTM3 genotype might regulate the effects of GSTM1.¹¹ In breast cancer, the incidence of breast cancer risk was probably caused by haplotypes of the GSTM3 gene cluster in the absence of GSTM1.⁶⁶ Another study proved the susceptibility to breast cancer among premenopausal women could increase if they simultaneously expressed the GSTM3*B and the GSTP1 genotypes. On the other hand, it also mentioned that the risk would increase fiercely if they lacked the GSTT1 at the same time.¹⁰ In colon cancer, the absence of GSTM3*B was a protective factor, especially in accordance with the null type of GSTM1. The genotype analysis of patients with distal and proximal tumors revealed that the constitution of the GSTM3*B allele and GSTM1-null were the most frequent genotypes.⁶⁸ In bladder cancer, individuals without the homozygous type of GSTM1 or GSTM3 were apparently sensitive to carcinogenesis.⁹ Besides, the “wild types” of GSTM3 or GSTM1 served as protective genotypes for bladder cancer. Taken together, this infers that GSTM3 can influence the incidence and risk of cancer solely or in combination with other genes such as GSTT or the GSTP family. However, because some personal data were absent in this review, we could not conduct more detailed analyses. We also analyzed the inner linkage of effects of GSTM3 with other risk factors. Even though the present conclusions for gene-gene analysis are not homogeneous, they obviously advocate that GSTM3 functions as a risk regulator, either individually or in cooperation with other polymorphic genes.

GSTM3 as a Prognostic Indicator in Pan-Cancer

The overall survival curves of GSTM3 are depicted in an online Kaplan–Meier (KM) plotter (www.kmplot.com).⁷³ This is a novel interactive website that evaluates gene expression and overall survival (OS) according to TCGA. Each

type of cancer corresponds to a different group of people. Median values for each cancer were selected as cutoff values to draw the KM plot. The connection between the GSTM3 mRNA level and the OS of cancer patients is shown in (Figure 3). From the available data, GSTM3 was shown to correlate significantly with OS in six malignancies (405 cases of bladder cancer, 371 cases of live hepatocellular carcinoma, 165 cases of rectal adenocarcinoma, 288 cases of renal clear cell carcinoma, 304 cases of cervical squamous cancer, 1090 cases of breast cancer). On the one hand, the high level of GSTM3 was significantly associated with poor OS in bladder cancer ($P=0.033$), live hepatocellular carcinoma ($P=0.0033$), and rectal adenocarcinoma ($P=0.0029$), indicating its tumor-promoting role. On the other hand, it serves as a tumor suppressor in RCC ($P=0.00049$), cervical squamous cancer ($P=0.041$), and breast cancer (0.027). The above results demonstrated that GSTM3 plays versatile roles in malignant tumors. Further exploration is much anticipated in terms of analyses of the differentiation, gender, age, and pathological stage on the prognostic value of GSTM3. Additionally, these results are derived from public databases and need to be verified by further studies. Due to the small sample size, the conclusions here should be regarded as preliminary or tentative until they are verified in extensive population-based research.

GSTM3 in ROS and Oxidative Stress

Oxidative stress reflects an imbalance between the production of ROS and antioxidant defense systems.⁷⁴ It exerts an important role in the pathological process of malignant tumors, hypertension, diabetes, and even neurodegenerative diseases.^{75–77} It is a conflict between antioxidant and oxidant balance, which results in cellular injury, and the imbalance may be caused by excessive ROS.^{78,79} ROS include superoxide anion, hydrogen peroxide, hydroxyl radical, amongst others, and are produced naturally by the activity of the mitochondrial electron transport chain.⁸⁰ It is known that cells have defense mechanisms to break down ROS by synthesis proteins binding to ROS and composing hydrophilic chemicals that are readily secreted. The antioxidant defense system can protect DNA from the damaging effects of oxidative stress.⁸¹ The GST family appears to be very significant in preventing cells from harmful endogenous substances.⁸² Particularly, GSTM3 could protect cells against electrophilic damage via catalyzing the conjugation of ROS and glutathione, playing a pivotal role in detoxification and ROS clearance.^{83,84}

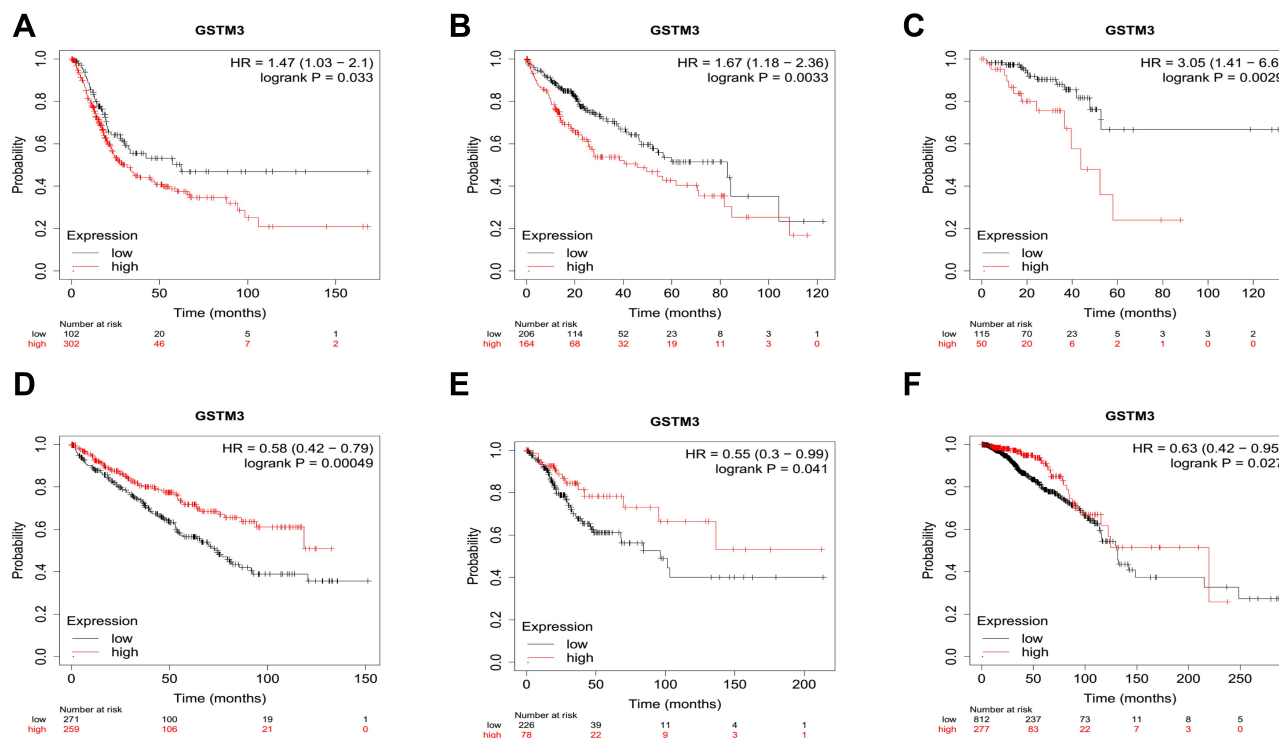


Figure 3 The overall survival curves of GSTM3 in different cancers depicted by KM plotter. **(A)** Bladder cancer. **(B)** Liver hepatocellular carcinoma. **(C)** Rectal adenocarcinoma. **(D)** Renal clear cell carcinoma. **(E)** Cervical cancer. **(F)** Breast cancer.

In a former study, Wang³² reported that GSTM3 served as a tumor suppressor by modulating the activity of ROS. The variant G allele of rs1055259 might elevate GSTM3 expression by affecting the binding of miR-556 and 3'UTR of the GSTM3 gene, resulting in low ROS levels and high thiol levels, and further suppressing the proliferation and invasion of RCC cells. Antioxidant capacity has been proven to be associated with GSTM3 regulation in RCC. Augmented ROS can initiate redox-linked signaling responses and irreversible injuries in RCC.^{85,86} Alteration of cellular redox balance in RCC might also be correlated with the expression of GST enzymes.⁸⁵ Shiota found that GSTM3 overexpression was accompanied by elevated ROS accumulation in castration-resistant PC cells. The polymorphism in GSTM3 alters the activity of antioxidant enzymes to contribute to hormonal resistance therapy through oxidative stress.³⁵ Besides, Li⁴⁶ found that downrated GSTM3 enhanced the production of ROS in glioma cells. Recently, GSTM3 was proven to play a crucial role in regulation of the oxidative stress and mitochondrial function in mammalian sperm.⁸⁷ Polymorphisms in antioxidant genes and the gene–gene interactions, such as GSTM3 rs3814309/NQO1, may increase the potential risk of

male infertility in the Chinese population.⁸⁸ Mechanically, Chu⁸⁹ pointed out that the domain-containing protein 1 (NSD1) regulates the expression of GSTM3 in response to oxidative stress. NSD1 was associated with oxidative stress by H₂O₂-induced. NSD1 suppression led to the reduction of GSTM3 levels through the –63A/C TATA box. Interestingly, Liu⁹⁰ provided strong proof that GSTM3–63A/C served as a potential target responding to oxidative stress. In a word, glutathione S-transferase mu3 has a strong antioxidant ability by resisting numerous harmful substances in the environment.

Conclusions and Prospects

As a significant component of the mu-class subfamily, GSTM3 exerts an important role in protecting cancer cells from oxidative stress and helps to prevent against carcinogens. It is also closely associated with cancer susceptibility and tumorigenesis as a result of polymorphism or aberrant expression. At the proteomic level, GSTM3 is closely involved in cell proliferation, tumor invasion, metastasis, chemoresistance, and even prognosis in different kinds of cancers. It also functions as an important intracellular radical scavenger and protects cells against

ROS. At the genetic level, genotyping of important alleles for GSTM3 gene mutations may lead to increased cancer risk. Polymorphisms exert an impact on individual sensitivity to certain pathologies.

In conclusion, the present article is the first comprehensive review of GSTM3 and discusses the mechanisms of GSTM3 in different malignancies. We systematically reviewed the biological functions and genetic polymorphisms of GSTM3 among pan-cancer and showed the promising future application of manipulating GSTM3 expression to improve clinical outcomes in patients with malignancy. Furthermore, the identification of the underlying mechanism can evolve into the foundations of therapeutic targets. In the field of research into GSTM3 and malignancies, convictive animal experiments and clinical studies are still insufficient to illustrate its role in the treatment of malignant diseases. Finally, the molecular mechanisms of GSTM3 in different cancers warrant further study. We strongly believe that GSTM3 could be a potential target in the future.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All of the authors declare no conflicts of interest in this work.

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