The role of genetic polymorphism of glutathione -S transferase in cancer development and anticancer drug resistance

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Abstract :

Glutathione S-transferse family is an antioxidant enzymes. This family of proteins is characterized by enzymatic and non-enzymatic properties that have rendered them an important factor in many metabolic processes, including internal and external origin detoxification , cell proliferation, apoptosis, and drug resistance. The genetic polymorphisms in glutathione s- transferase affect the biologic activity of this enzyme and thus affect its role in the metabolic pathways that participates in it and make subjects vulnerable to many of the cancerous diseases that have been addressed here. In addition, genetic polymorphism of GST may affect on the response of the patients to anticancer drugs.

Keywords: genetic polymorphism , GST ,Cancer , drug resistances

عنوان البحث: دورالتغيرات الجينية لانزيم الكلوتاثيون اس تراسفريس في تطور مرض السرطان وفي مقاومة العلاج

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مفتاح البحث : التغيرات الجينية ، كلوتاثيون اس ترانسفيريز ، السرطان ، مقاومة الدواء

الخلاصة :

يعتبر انزيم الكلوتاثيون اس- ترانسفريز من الانزيمات المضادة للاكسدة . تمتاز هذه العائلة من البروتينات بامتلاكها صفات انزيمية وغير انزيمية جعلت منها عامل مهم في العديد من العمليات الايضية ومن ضمنها ازالة السموم الداخلية والخارجية المصدر وتكاثر الخلية وموت الخلية المبرمج ومقاومة العلاج . ان التغيرات الجينية في انزيمات الكلوتاثيون اس- ترانسفريز بانها تؤثر على الفعالية البايلوجية للانزيم وبالتالي تؤثر على دوره في العلمليات الايضية التي يدخل فيها وتجعله عرضة للعديد من الامراض السرطانية التي تم التطرق لها هنا بالاضافة الى ان التغيرات الجينية للانزيم تؤثر على استجابة المريض للادوية المضادة للسرطان .

Introduction

Glutathione S-Transferases

The glutathione S-transferases (GSTs) are crucial enzymes, which belong to the phase II drug metabolizing enzymes. These are known to have an important part in detoxifying xenobiotic in the environment after consumption along with harmful substances such as those which promote carcinogenesis. In addition, GSTs enzymes can be helpful in decreasing the negative effects of drugs, xenobiotics and oxidative stress products. The mechanism involves protecting the cell against multiple exogenous and endogenous substances, catalyzing the reactions of glutathione with a number of other substances, including those with genotoxic proportions (1,2).

Functions of GSTs

GSTs are known to have both, enzymatic and nonenzymatic properties. These enzymes are a part of several cellular procedures, for instance, they are utilized in phase II metabolisms, stress responses, cell proliferations, apoptosis, oncogenesis, tumor progressions and even drug resistance . In terms of their non-enzymatic properties, this comprise the GSTs interacting with cellular proteins. Typical examples of these interactive proteins include: c-Jun N-terminal kinases (JNK), TNF receptor associated factors (TRAF), Activator of S phase kinase (ASK), Protein kinase C (PKC) and Transglutaminase 2 (TGM2). Over the course of interactions, these proteins either undergo a functional modification or the GST protein is post translationally altered. These functions are discussed in detail in the following section.

I-Detoxification

GSTs are able to detoxify several harmful substances. These include reactive oxygen species (ROS) or even xenobiotics (3). GSTs can catalyze reactions concerning the conjugated chemical compounds with exo and endogenous origins along with glutathione (4, 5). This process aids in detoxifying products formed by the oxidative degradation of lipids, groups of eicosanoids, several kinds of chemotherapeutic agents beside the harmful substances which promote carcinogenesis, for instance the heterocyclic aromatic amines (6). The reason for conjugating electrophilic reagents with reduced glutathione is to ensure that there is a possible reduction in the likelihood

of any poisoning to vital cell components, such as proteins or nucleic acids, because of the strong reactive compounds. In addition, GSTs are able to protect DNAs against any oxidative damage that may cause mutations, consequently leading to carcinogenesis (7).

II- Toxification due to glutathione conjugation

Often, it is noticed that the -glutathionyl conjugate can be more lethal than the source compound. This has potential drawbacks in treating cancers. To elaborate, for some substrates such as benzyl and phenethyl isothiocyanates, GSTs are able to catalyze both, progressive and backward reactions. This can lead to greater poisoning instead of detoxifying (8).

III- SE- independent GSH peroxidases

There are a few GSTs which have been observed to show secondary catalytic reactions involving the activities of Selenium-Independent Glutathione preoxidases. This includes the reduction of organic hydroperoxides to the corresponding alcohols (9). GSTs are capable of reducing chemical species such as fatty acids, phospholipids along with DNA-hydroperoxides produced due to the oxidative damage (10).

IV- Isomerase activities

GSTs are able to perform catalysis on the cis-trans isomerisation of maleyl acetone to fumaryl acetone along with maleyl acetoacetic acid to fumaryl acetoacetic acid (11).

V- GSTs as ligandins

Glutathione tranferases, also called ligandins, were initially recognized as cytoplasmic proteins which have the ability to bond with several chemical species. These include hormones, bilirubins, haeme, fatty acids and penicillin. The bonding process takes place through covalent and non-covalent connections. Literature shows that there has been an increasing interest in the “ligandin” function of GSTs. Further, this process is able to contribute to the intra-cellular sequestering and transportation of xenobionts as well as hormones (12, 13).

VI- GSTs and kinase regulations

GSTs have an important role in the cellular signaling process. They form the protein-protein interactions with crucial kinases included in regulating the stress responses, apoptosis and proliferations (14).

Classes of GST genes

GSTSs are present commonly in the environment with their major presence in eukaryotes and prokaryotes. They exist in these organisms as the fundamental phase II enzymes for the metabolic detoxifying processes (15). Human beings also have GSTs in their systems where the enzymes are distributed in three main groups of proteins. These are cytosolic, mitochondrial and preoxisomal (k class) along with microsomal GSTs.

There are eight human cytosolic GSTs which are classified into 8 classes (designated with Greek letters α, ζ, θ, μ, π, ς, τ, and ω) and 6 isozymes of a group of membrane-associated family of proteins from classes I, II, and IV of the MAPEG (membrane-associated proteins in eicosanoid and glutathione metabolism) (1, 16).

Polymorphism of GSTs

GSTs have been found to have several incidences of polymorphism in their classes. To be specific, the M and T classes of GSTs have no phenotypes *(*GSTM*0 and GSTT*0*)* while humans do not have catalytically active proteins. In terms of the GSTM1*0 allele, this is found to be in approximately 40-60% of Caucasian people. Also, it is linked with a rise in several cancerous diseases concerning various vital body parts such as lungs, prostates, bladder, head and neck. The GSTT*0 phenotype differs amongst varying ethnicities with the most occurrence in Chinese (i.e. nearly 65%) and the least occurrence in Mexican Americans (i.e. nearly 9%). This phenotype is also linked to a rise in risk of tumors concerning vital body parts such as the head, neck, oral cavities, pharynx, and larynx. The GSTM1 gene consists of 4 alleles and is the one, which has been extensively reviewed up till now. GSTM1 polymorphism M1*A 0.2 is linked to a reduced risk of bladder and breast cancers in the Caucasian populations. M1*B 0.2 is consequently linked with a reduced risk of pituitary adenomas while M1*0 0.59 has the ability to enhance the risks of lung, colon bladder and breast cancers. Further, GSTM1*A is known to be linked with reduced risks of bladder

cancers with a presence of an allele of a frequency of 20%. Studies have revealed that about 10 – 20% of the Caucasians are carriers of the GSTP1 null genotype. Moreover, the GSTP1 gene polymorphism is usually a point mutation SNP (single nucleotide polymorphism) within exon 5 Ile105 Val. Hence, resulting mutations are GSTP1genotypes Ile/Ile, Ile/Val and Val/Val. Also, the interactions between isoleucines and valines in the amino acids leads to reduced activities of the proteins in terms of the enzyme's function(17).

Genetic polymorphism at the GSTP1 locus results in 4 alleles, i.e. GSTP1*A, GSTP1*B, GSTP1*C and GSTP1*D. These are known to vary in terms of their structures and functions. The promoting zone consists of a TATA unit accompanied with two SP1 sites along with insulin response and antioxidant response components, surrounded by an AP1 site. GSTP1*A has an important part in the attainment of resistances to cisplatin (CDDP) by improving the ability of the cells to produce platinum GSH conjugates / CDDP-GSH adducts. GSTP1*B refers to an allele where a single nucleotide (A→G) replacement at a known position consequently reduces catalysis. In treating cancer patients, homozygosity for GSTP1*B is favourable(17). This is due to their reduced abilities in detoxifying platinum-based anti-cancer agents. In terms of GSTP1*C, it is an allelic variant which predominates in malignant glioma cells. It also varies from various GSTP1 variants by two transitions leading in the formation of Ile104Val and Ala113Val(17).

The Alpha(A) class family consists of 5-functional genes (i.e. GSTA1 to GSTA5) and 7 pseudo-genes located in a clustered mapped to chromosome (18). Gluathione S-transferase A1 polymorphisms are known by 3 connected SNPs that lead to a differentiating expression with a low transcriptional activation of the variant GSTA1*B (−567G, -69T, -52A) compared to the usual GSTA1*A allele (−567T, -69C,-52G) (19).

Polymorphism linked to a reduced expression of the GSTA1 enzyme can result in the build-up of carcinogenic substances in human bodies, which can then lead to a rise in the development of cancers (20). For instance, due to GSTA1*B's ineffective detoxifying abilities, it is linked to colorectal cancers. To elaborate, it is unable to successfully detoxify 2-amino-1-methyl-6-phenylimidazo[4,5-b]-pyridine. Moreover, this allele has been found to be at a 38 – 50% frequency in the Caucasian population (21). Also, noteworthy works in the past have shown the linkage of polymorphism in

GSTA1 gene to several diseases. These include colorectal cancers, deaths due to cardiovascular diseases, Hepatitis B viruses and acute myeloid leukemia (19, 22).

In terms of the 4 polymorphisms (i.e. GSTZ1*A–D), these are specifically known as GSTZ1*A (Lys32; Arg42; Thr82); GSTZ1*B (Lys32; Gly42; Thr82); GSTZ1*C (Glu32; Gly42; Thr82); GSTZ1*D (Glu32; Gly42; Met82). While GSTZ1*A is known to have the uppermost catalytic activities, GSTZ1*D is known to be linked to inaccuracies in tyrosine metabolism reactions in addition to enzyme mutations. Further details of such inaccuracies can be found in Rodent's model for GSTZ1 (23).

GST polymorphism and pre-disposition to cancers

Identifying hereditary genetic variations, which can have an effect on the occurrence of major diseases, was made simpler due to the Human Genome Project. Hypothesizing the variation in diseases has led to a drive in evaluating various gene variants for determining their linkage to the physiological properties in humans. This also helps in analyzing the commonly occurred chronic diseases as well as an individual's response to drugs. Several gene variants can be utilized for the metabolism of carcinogenic substances. This would result in a somewhat metabolizing process, which can lead to the successful exposure of a disease. Hence, several works in the past have shown the wide-ranged genetic variation in metabolic genes among races or ethnicities. However, until today there is no agreement regarding the impact factor in terms of the disease risks. Furthermore, identifying gene aspects, which underlie such detrimental diseases is challenging. This is due to the influence of gene variants and other environmental aspects. Moreover, it has been shown in the past that patients who had identical mutations, varying genetic factors along with environmental factors and lifestyle choices demonstrated influential roles. While a small proportion of researches are available on the genetic determinants of cancer, other works have revealed the influential abilities of GST polymorphism in cancers. This is based on their part, which involves modulating the biological effects of carcinogenic substances. Hence, noteworthy literature available regarding this, which discussed the relationships between GST genetic variants with cancer risks (24) is mentioned in the next section.

Breast cancers

Breast cancer (BC) is the center of several research works, which aimed to elucidate some genetic aspects. Researchers linked successfully GST polymorphism with the increased risks of acquiring BC. BC is known to occur in a number of women around the globe. To elaborate, mutations in genes such as BRCA 1-2 and p53 are known to present an increased risk for developing BCs. However, the occurrence of these particular alleles is rather low. Nevertheless, mutations in xenobiont genes are known to have increased allelic occurrences (24).

A well-known BC previous study, which examined several African-Americans along with White Americans revealed positive gene associations. The work showed women with GSTM1 null obtained an OR of 2.1. Whereas, in women who were carriers of GSTT1 null, the OR was 1.9 (25). Furthermore, a study by Mitrunen et al. (2001) linked polymorphisms due to GSTM1, GSTM3, GSTP1 and GSTT1 with the increased risks of BCs. The work showed a positive linkage with GSTM1 null, (i.e with an OR of 1.5) and GSTM3*B allele. In terms of the GSTP1 Ile105/Ile105 genotype, the OR was 2.07, which was much higher in women with GSTT1 null, where the risk was strongly increased with an OR of 9.93(26). Furthermore, Gudmundsdottir et al. (2001) also studied a couple of patients, their study confirmed a positive linkage of GSTT1*A carriers along with p53 mutations in all cases and controls (27). It is worth mentioning that studies, which are looking into cancers, mainly concentrate on the GSTM1, GSTT1 and GSTP1 genes. A study showed that GSTA1*B polymorphism has a strong negative linkage with breast cancer along with GSTO2*B (28). Conversely, GSTO1*BB genotype had increased risks of breast cancers if comparisons were made with GSTO1*AA genotype carriers where the IRR was 1.62. This linkage was considered powerful with regards to the estrogen receptor, which has an IRR of 2.16 (29).

Gastric cancers

While earlier works confirmed that Helicobacter pylori is the main contributor to most gastric cancers (GC), it is also known that genetics also play a role in GCs. However, most research works in the past on genotypes GSTM1 and GSTT1, failed to show the correlation of these genes to the risk of developing GCs (30). Nevertheless, a study has appeared in the literature, which considered a group of patients suffering from GCs along with some control subjects. The study confirmed a 1.48 fold risk in patients

with a genotype of GSTT1 null. However, this was not the case with genotypes GSTM1, GSTM3 or GSTP1. Moreover, an interesting research finding revealed that young individuals of GSTT1 null genotype had a greater risk of developing GCs (i.e. with OR of 3.85) (31). Another study on healthy and patients suffering from GCs showed that individuals with a genotype of GSTM1 null had a greater risk of developing GCs (i.e. with OR of 1.98). In addition, it was found that individuals who tend to smoke or consume highly salted tea were also at a greater risk of developing GCs (i.e. with OR of 8.98) (32). On the contrary, previously some researchers have performed investigative works to confirm that individuals with null genotypes of GSTM1 and GSTT1 show a potential decrease in the risk of developing GCs (33). Furthermore, a study on carriers of GSTM1 null in combination with IL-1RN*2 polymorphism showed that these individuals demonstrate an increasing risk of developing GCs. Researchers suggest that the change in cellular IL-1RN along with anti-oxidative properties of GSTM1 may result in the predisposition of a high risk of developing GCs (28). It is worth mentioning that previously some researchers have attempted to show an association between GSTM1 and GSTT1 to the risk of developing GCs. A study confirmed this with stating that GSTT1 null carriers tend to have an OR of 2.58 while carriers of both the above-mentioned genotypes have an OR of 3.32 for developing GCs. An interesting finding showed that GSTP1*BB genotype carriers had a protecting effect in developing GCs with an OR of0.20 (34). A meta-analysis study revealed that for Asian population, CYP2E1 PstI/RsaI polymorphisms may result in the risk of developing GCs. Additionally, the study also demonstrated that a synergic relation between GSTM1 and CYP2E1 may lead to developing GCs (35).

Lung cancers

Lung cancer (LC) is known to be the foremost cause of death due to cancers globally. LCs result in 1.3 million deaths, annually (36). GSTP1 is a common genotype, which is present in pulmonary tissues. The metabolic agent of this genotype is present in cigarette (37). A detailed analysis showed that GSTP1*B does not have an association with developing LCs, regardless of ethnicities. Further, the study showed that individuals who were carriers of Val105 had an OR of 1.11. Considerations made on ethnicities, ages and genders along with smoking preferences showed that a greater

risk of developing LCs was present in the Asian population who had GSTP1*B. This was not the case in the White population (38). However, a study on healthy individuals and patients who had LCs revealed that GSTP1*B had no correlation to developing risks for LCs with an OR of 1.02. however, stratifying the presence of GSTP1*B by ages showed that young individuals (i.e. people with an age of less than 50 years) had a positive correlation between the consumption of tobacco and developing LCs with an OR of 2.67 as compared to older people who had an OR of 0.87 (39). Furthermore, various works presented a correlation between the consumption of tobacco with developing LCs in individuals who had GSTM1 and GSTT1 null genes. Another study on the Asian population revealed that there is an increasing risk in developing LCs among these people who are also GSTM1 and GSTT1 null gene carriers, with an OR of 1.31 and 1.49, respectively. These works did not take into consideration any linkage between GSTP1*B and the risk of developing LCs (40). As well as other researchers study the correlation between CYP2E1, GSTM1 and GSTT1 genotypes with tobacco consumption and developing LCs. The work confirms that smokers tend to have a greater risk of developing LCs, in terms of the specific genes, it shows that individuals with GSTM1 null had a greater risk for LCs with an OR of 1.9 (41). In terms of Asians, another study on several cases and controls demonstrated a positive correlation between GSTT1 null and developing in LCs with an OR of 1.28. However, this was not the case in the Caucasians, who had an OR of 0.99. No major association was noted between GSTT1 and consumption of tobacco on developing LCs (42).

GST and colorectal cancers

A great amount of reviews exist on the single nucleotide polymorphism (SNP) of GST genes as a risk modulating factors in various kinds of cancers. This also includes gastro-intestinal cancers. SNPs are known to have an influence on the functionality of GST-enzymes at both levels, genes and proteins. This then results in affecting the detoxifying procedure of carcinogenic substances, thus the levels of DNA damages. It may also have a secondary effect on the risk of developing cancers (43). The findings of the researchers who studied the relationship between GST gene polymorphism and the risk of colorectal cancers were conflicting, some of them supported a strong relationship

between them, whereas the other studies does not mention the relationship between GST gene polymorphism and the risk of colorectal cancers.

GST polymorphisms and tumor drug resistances

Humans GSTS usually host polymorphism, mainly SNPs and are less often involved in GSTP1 and GSTA1 genes with the deletion in GSTM1 and GSTT1 genes. The association between polymorphism and cancer therapies is at the moment an interesting research area, which is mainly focused at GST classes α, μ, π and θ (44). Recently, works in this field have showed that analyzing polymorphisms of multiple classes of GSTs simultaneously may associate with a therapeutic outcome as compared to singular genetic works. Such approaches may be able to better understand that several types of cytosolic GSTs are sharing an over-lap with substrate specificities. Hence, the absence of one GST isoform can be replaced with an increase of another type of GST. Moreover, cancer patients are usually given anti-cancer agents for treatments. These may be differentially metabolised by various GSTs. A polygenic approach to this would involve achieving innovative and updated results, specific to the GST null genes, GSTM1*0 and GSTT1*0. To elaborate, studies have demonstrated that the combination of GSTM1*0 / GSTT1*0 or GSTM1*0 / GSTP1Val105 genes was linked to an increase response rate along with better survival chance in patients suffering from ovarian cancers (45, 46). Furthermore, it was found that those patients who had brain tumors with genotypes GSTP1*A and GSTM1*0 combined, were able to survive for longer period, comparatively. In terms of nitrosourea, it was shown that a combination of these genes led to an improved prediction of incidences indirectly related to chemotherapy (47). Interesting and successful findings along with potential drawbacks of various genotypes has resulted in pharmacogenomics to consider analyzing a greater number of genes, which may have an influence on the whole genome system. A better approach for GSTs would involve the utilization of linkage disequilibrium based analysis. This would allow for the usage of a minor subset for tagging SNPs to address diversities.

Conclusion

This review offers improved understandings of the role of GST genotype superfamily in cancer and their clinical importance.Reasonably, this shall ease the incorporation of expression and polymorphism while managing cancers in patients and would develop a GST-targeted cancer therapeutics.

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