THE EFFECT OF GLUTATHIONE S-TRANSFERASES GENE MUTATION ON DIFFERENT MALIGNANT DISEASES

Essay

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AFBO	**:**	Aflatoxin B١-٨,٩-epoxide.
AFQ١	**:**	Aflatoxin Q١.
ALL	**:**	Acute lymphoblastic leukemia.
CaP	**:**	Cancer prostate.
CNDB	**:**	١-chloro-٢,٤-dinitrobenzene.
ELISA	**:**	Enzyme linked immunesorbent assay.
GSH	**:**	Reduced glutathione.
GSTs	**:**	Glutathione-S-transferases.
HBV	**:**	Hepatitis B virus.
HCC	**:**	Hepatocellular carcinoma.
HCV	**:**	Hepatitis C virus.
PAH	**:**	Polycyclic aromatic hydrocarbons.
RIA	**:**	Radioimmunoassay.
ROS	**:**	Reactive oxygen species.
tGSTs	**:**	Total Glutathione-S-transferases.
TR-IFMA	**:**	Time resolved immunoflurometric assay.

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INTRODUCTION

Glutathione S-transferase (GSTs) play an important role in the metabolism of environmental carcinogens like polycyclic aromatic hydrocarbons and heterocyclic aromatic amines, which are well-known carcinogen **(Gammon et al., ٢٠٠٢).** GSTs also play an important role in the metabolism of estrogen and lipid peroxidation **(Florian et al., ٢٠٠٤).**

In humans, five classes of GST enzymes have been identified which are the α, μ, σ, Л, ɵ classes. Each class is encoded by a separate gene or gene family. GSTM١ gene codes for GST- μ١ isoenzyme and GSTT١ gene codes for GSTΘ١ isoenzyme **(Ates et al., ٢٠٠٥).**

The GSTM١ and GSTT١ genes both exhibit deletion polymorphisms, called GSTM١ and GSTT١ null genotypes **(Vogl et al., ٢٠٠٤).** A decrease in GST enzyme activity could result in inefficient detoxification of various carcinogens, which could lead to genetic damage and increase cancer risk **(Gudmundsdottir et al., ٢٠٠٤)**. The most commonly encountered tumours are breast cancer, hepatocellular carcinoma, lung cancer, basal cell carcinoma, prostatic cancer and colorectal cancer **(Ates et al., ٢٠٠٥).**

AIM OF THE WORK

The aim of the present study is to evaluate the effect of GSTM١ and GSTT١ genetic polymorphisms on the occurrence of various malignant diseases.

I. GLUTATHIONE-S-TRANSFERASES

Glutathione-S-transferases (GSTs) are a family of multifunctional detoxifying enzymes that catalyze the conjugation of glutathione with large number of electrophilic xenobiotics, such as chemical carcinogens, environmental pollutants, and antitumor agents **(Hayes et al., ٢٠٠٥).**

A. Chemistry of Glutathione S-Transferase:

Glutathione s-transferase consists of a supergene family of dimeric isoenzymes whose individual members are composed of various combinations of different monomers (subunits with molecular weights ranging from ٢٠-٢٥ KD) **(Zheng et al., ٢٠٠٢)**. For many years, the nomenclature was based on the type of substrate conjugated, i.e., glutathione S-transferase for ٣,٤-dichloro-nitrobenzene and glutathione S-alkyltransferase for methyl iodine. It then became clear that although a number of different glutathione transferases existed, certain substrates were utilized by more than one enzyme protein and so the classification based on the substrate became not appropriate. Subsequently, the nomenclature was based on the reverse order of their elution from a chromatographic cellulose column **(Park et al., ٢٠٠٠).**

In all mammalian species, the total glutathione-S-transferase (t-GST) is represented by a large number of isoenzymes. They have different substrate specificities, immunological cross reactivities, amino acid composition and terminal amino acid sequence data. The difference in amino acid composition and specific enzyme activiy, suggest that each of these isoenzyme classes is the product of distinct genes **(Zheng et al., ٢٠٠٢).** The human species possess at least twenty-one GST genes of which fifteen encode soluble transferases and six for membrane-bound transferases **(Townsend and Tew, ٢٠٠٦).**

B. Families of GSTs:

Board et al. (٢٠٠٠) added that there are three mammalian GST families, namely cytosolic, mitochondrial, and microsomal GST. Cytosolic GST isoenzymes are broadly cytoprotective, whereas microsomal proteins have proinflammatory activities**.**

Cytosolic human GST exhibit genetic polymorphisms and this variation can increase susceptibility to carcinogenesis and inflammatory diseases **(Gart et al., ٢٠٠٤)**. Diol-epoxides derived from polycyclic aromatic hydrocarbons (PAH) pro-carcinogens are substrates for both GST Pi and GST Mu . Other

substrates for the cytosolic GSTs include the steroids, alkenes and quinines **(Hayes et al., ٢٠٠٥)**.

Microsomal GSTs are structurally distinct from the cytosolic in that they homo-and heterotrimerize rather than dimerize to form single active site. They have activity against a broad range of other substrates, including styrene ٧-٨- oxide, ١-chloro-٢,٤ dinitrobenzene and cumene hydroperoxide . Furthermore, various halogenated alkenes are metabolized preferentially by microsomal GSTs compared to the cytosolic forms **(Hayes et al., ٢٠٠٥)**. Also they are involved in production of leukotrienes and prostaglandin E, it follows that members of this superfamily constitute important drug targets regarding asthma, inflammation and the febrile response ***(Schmidt et al., ٢٠٠٠)***.

Mitochondrial GSTs protect against mitochondrial injury during the secondary phase of oxidative stress. However, other properties of mitochondrial GST, such as conjugation of environmental chemicals and binding of lipophilic non-substrate xenobiotics and endogenous compounds, remain to be investigated **(Townsend et al., ٢٠٠٦)**.

C. Isoenzymes of GSTs:

In the year ٢٠٠٠, it was proved that the human cytosolic GST superfamily contains eight distinct classes or isoenzymes, namely :Alpha, Mu, Pi, Theta, Sigma, Kappa, Zeta and Omega, based on their structural and functional properties, with Mu being the most widely expressed. Each class comprises one or more distinct gene products, with different although overlapping substrate specificities **(Park et al., ٢٠٠٠)**.

١. GST-Alpha:

GST alpha is the major basic form of GSTs. Its isoelectric focusing occurs at pH ٧,٥-٩. It is a relatively small isoenzyme with a molecular weight of ٥٠ Kd**.** There are at least two classes of GST-alpha that are the products of two separate gene loci. The chromosomal location of the genes that encode these human alpha-classes has been investigated using in situ hybridization techniques. Separate studies have indicated that the genes are clustered on the short arm of chromosome ٦ at band p١٢ **(Sun et al., ٢٠٠١).**

٢. GST-Mu:

It is a neutral isoform of GST. The characteristic features of this isoenzyme are its high activity towards the substrate

trans-٤-phenyl-٣-bute-٢-one and its isoelectric focusing occurs at neutral pH (٦-٦,٥)**.** It is present in small quatities in human hepatocytes. GST-mu is subject to polymorphism and is expressed in only ٦٠٪ of the general population. The absence of GST-mu activity is caused by inheritance of two null allele genes **(Park et al., ٢٠٠٠).**

٣. GST-Pi:

It is the placental form of GST. GST-Pi is a group of isoenzymes with protein combining ability. Also, it is the major form of acidic GSTs, its isoelectric point occurs at PH ٤,٥-٤,٨. Its molecular weight is ٢٥ kd. It has been purified from three primary human tumors, namely malignant melanoma, mesothelioma and breast carcinoma **(Guo et al., ٢٠٠٠)**.

GSTpi is the most prevalent isoenzyme of the human GST family being expressed in almost all tissues mainly the breast. GSTpi gene expression is heterogenous, with the lowest levels being found in the liver, and the highest levels being found in the lung, esophagus, placenta and breast **(Hayes et al., ٢٠٠٥).**