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GLUTATHIONE S-TRANSFERASES: A BRIEF ON CLASSIFICATION AND GSTM1-T1 ACTIVITY

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ABSTRACT: The glutathione S-transferase (GST) isoenzyme superfamilies detoxify a wide-range of toxic chemicals and environmental substances are extensively expressed in mammalian tissues. Liver and pancreas are the sites where cytosolic Phase I and phase II biotransformation GSTs enzymes have characteristic expression. GSTs play a key role in the deactivation of reactive oxygen species (ROS) and the metabolism of lipids, chemotherapeutic agents. GSTs are mainly involved in conjugation of reduced glutathione (GSH) with diverse substrates specificity and it is possible that genetic variations in these enzymes will influence cellular response to the environmental agents. GSTs are overexpressed in response to a chemical or oxidative stress as an adaptive physiology and upregulated in cancerous state of organ or tissue. GSTs are essentially involved in susceptibility to various forms of cancer as they are vital in detoxification mechanism to metabolize the environmental carcinogens. GSTM1 encodes for a class mu GST isoenzyme involved in polycyclic aromatic hydrocarbons (PAHs) detoxification. The substrates of GSTM1 include benzo(a)pyrene, benzo(c)phenanthrene, benzo(g)chrysene and other carcinogens. They can catalyze *in-vitro* GSH conjugation with several potent carcinogenic epoxides including aflatoxin B1(AFB1)8,9-epoxide and electrophilic metabolites of PAHs present in tobacco smoke. Ethylene dibromide, p-nitrobenzyl chloride, p-nitrophenetyl bromide, methyl chloride, and methyl iodide, are known substrates for GSTT1 or GST Theta (θ). GST Theta is most primitive among other known GSTs and widely expressed in nature.

INTRODUCTION: The glutathione S-transferase gene family encodes genes for detoxification mechanisms. GST play an inimitable role in biotransformation of drugs and detoxify a number of endogenous and exogenous electrophilic lipophiles. [1] In response to a chemical or oxidative stress or they are overexpressed as a part of adaptive mechanism and upregulated during cancerous state.

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GSTs are essentially involved in susceptibility to various forms of cancer as they are vital in detoxification mechanism to handle the environmental carcinogens. [2] GST is involved in conjugation of reduced glutathione (GSH) with diverse substrates and it is possible that genetic variations in these enzymes will influence cellular response to the environmental agents. Also GST super families exhibit some redundancy i.e. the overlap in substrate specificity of individual isoenzymes. [3]

The active soluble cytosolic GSTs enzyme exists as a dimeric protein of two subunits approximately 25 kDa. [4, 5] The GSH-binding and the hydrophobic substrate-binding sites have been called the G- and H-sites, respectively. [6]

1-chloro-2, 4-dinitrobenzene (CDNB) is a universal substrate of GST and they are able to catalyze conjugation of reduced glutathione (GSH) with the aryl halides, 1,2-dichloro-4-nitrobenzene and bromosulfophthalein. [7, 8] GSTs also conjugate isothiocyanates, which are potent inducers of enzymes that detoxify environmental mutagens. [9] The conjugation process diverts the isothiocyanates from the enzyme induction pathway into excretion, leading to elimination of these anticarcinogenic substances and thus decreasing their potential chemopreventive effect. [10, 11, 12] They may also play a role in the metabolism of lipids, chemotherapeutic agents and reactive oxygen species.[13]

Classification of GSTs: The glutathione S-transferases (EC 2.5.1.18) are isoenzymes superfamilies that detoxify toxic substances are widely distributed in nature. [14, 15] Classified under two distinct categories, the larger superfamily include cytosolic, soluble, dimeric enzymes that are involved in biotransformation of toxic xenobiotics and endobiotics. [16, 17, 18, 19, 20] The other superfamily involves microsomal GST probably trimeric in structure and known as membrane-associated proteins in eicosanoid and glutathione (MAPEG) metabolism, primarily involved in arachidonic acid metabolism. [21]

On the basis of their primary structure the human cytosolic/soluble GST superfamily contains at least 16 genes subdivided into eight separate classes designated α(GSTA), mu(GSTM), π(GSTP), θ(GSTT), T(GSTZ), σ(GSTS), o(GSTO) and k(GSTK), each of which contains one or more of the homodimeric or heterodimeric isoforms.[15, 22, 23, 24]

Tissue and organ localization: GSTs are widely expressed in mammalian tissues with a broad substrate specificity. [3] Many of the cytosolic Phase I and phase II biotransformation GST enzymes are characterized by zone-specific expression in the liver and the pancreas validate their role in detoxification. [25, 26] GST are active in normal breast tissue to protect against damage caused by reactive metabolites of chemicals, such as estrogen semiquinone and estrogen 3,4-quinone. [27]

GSTM1 activity: GSTM1 encodes for a class mu GST isoenzyme involved in polycyclic aromatic hydrocarbons (PAHs) detoxification. The substrates of GSTM1 include benzo (a) pyrene, benzo (c) phenanthrene, benzo (g) chrysene and other carcinogens. [28, 29] They can catalyze *in-vitro* GSH conjugation with several potent carcinogenic epoxides including aflatoxin B_1-8, 9-epoxide and electrophilic metabolites of PAHs present in tobacco smoke. [30, 31] Members of mu and alpha GST superfamilies possess selenium-independent GSH peroxidase activity toward organic hydroperoxides for that Cumene hydroperoxide (CuOOH) is used as substrate suggesting that these enzymes may play a role in protection against highly reactive products of oxygen metabolism including those induced by asbestos.[32]

Glutathione peroxidase prevents intracellular macromolecules from free radicals during oxidative stress and its potential *in vivo* substrates are the hydroperoxides of phospholipids, fatty acids and DNA. [1, 15, 21, 32, 33, 34, 35, 36] Class alpha, mu and pi GST can detoxify harmful bulky aryl halides, ß unsaturated carbonyls including acrolein which is present in cigarette smoke [15], 4-hydroxynonenal which is produced by lipid peroxidation [37, 38], adenine and thymine propenals that are generated by oxidative damage to DNA [34], and aminochrome, dopachrome and noradrenochrome the quinine containing oxidation products of catecholamines. [39]

GSTT1 activity: Glutathione S-transferase theta (θ) is considered the most ancient of the GSTs. [23] The encoded GSTT1 human subunit is about 25,300 Da and the gene is 8.1 kb long. [40, 41] GSTT1 enzymes show lower glutathione binding activity, with increased catalytic efficiency as compared with other GSTs. [42, 43] However, GSTT1-catalyzed reactions can also increase the toxicity of some important small dihaloalkanes such as dichloromethane. [23] GSTT1 also catalyzes the detoxification of oxidized lipids and DNA. [43, 44] Halogenated organic compounds, for example, the ethylene dibromide, p-nitrobenzyl chloride, p-nitrophenethyl bromide, methyl chloride, and methyl iodide are known substrates for GSTT1. [45, 46, 47, 48] Class Theta GSTT1-1 is involved in GSH-dependent activation of dibromoethane (DBE).

In particular, GSTT1-1 can activate dichloromethane (DCM) by conjugation with GSH to form a reactive S-chloromethylglutathione. [49] DCM is an important compound widely used as a paint stripper, and in the synthesis of plastics and pharmaceutical drugs.

TABLE 1: CLASSIFICATION AND ORGAN LOCALIZATION OF GLUTATHIONE S-TRANSFERASES

Super Family	Class	Chromosome	Protein	Organ
Soluble	Alpha	6p12	GSTA1	testis=liver>>kidney=adrenal>pancreas
			GSTA2	liver=testis=pancreas>kidney>adrenal>brain
			GSTA3	Placenta
Soluble	Kappa	-	GSTA4	Small intestine=spleen>liver=kidney>brain
			GSTK1	liver (mitochondria)
Soluble	Mu	1p13.3	GSTM1	liver>testis>brain>adrenal=kidney>lung
			GSTM2	brain=skeletal muscle=testis>heart>kidney
			GSTM3	testis>>brain=small intestine>skeletal muscle
			GSTM4	brain, heart, skeletal muscle
			GSTM5	brain, heart, lung, testis
Soluble	Pi	11q13	GSTP1	liver, brain>heart=lung=testis>kidney=pancreas
Soluble	Sigma	4q21-22	GSTS1	fetal liver, bone marrow
Soluble	Theta	22q11	GSTT1	kidney=liver>small intestine>brain=prostate
			GSTT2	liver
Soluble	Zeta	14q24.3	GSTZ1	fetal liver, skeletal muscle
Soluble	Omega	10q23-25	GSTO1	liver=heart=skeletal muscle>pancreas> kidney
MAPEG	Microsomal	12p13.1-13.2	MGST-I	liver=pancreas>prostate>colon=kidney>brain
		9q34.3	MGST-I-Like I	testis>prostate>small intestine=colon
		4q28.31	MGST-II	liver=skeletal muscle=small intestine>testis
		1q23	MGST-III	heart>skeletal muscle=adrenal gland, thyroid
		5q35	LTC_4S	platelets=lung>liver
		13q12	FLAP	lung=spleen=thymus=PBL>>small intestine

Table developed from- Hayes, J. D. and Strange, R. C, 2000

Evolution: Significant homology between a class theta GST and a dichloromethane dehalogenase enzyme from the prokaryote *Methylobacterium* is suggestive of the fact that ancestral progenitor for mammalian GSTs probably arose from the theta class. [50] Membrane-bound GST enzymes represent examples of convergent, rather than divergent, evolution. [51]

CONCLUSION: Research on glutathione S-transferase family of enzymes possesses a huge scope in clinical genetics due to their association with many of the incurable life threatening diseases. There classification and organ localization through expression studies has given a way for more specific investigation. Molecular genetics with advanced DNA sequencing techniques have added a strong knowledge to their physiological network at molecular level.

More research equipped with advanced tools is required to be performed at populations and at individual level in order to provide a deep insight for personalized medicines.

CONFLICT OF INTEREST: Author declares no conflict of interest.

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