Mini Review

Pharmaceutical BIOPROCESSING

Human Glutathione Transferase Structure, Function, and Implications in Health and Disease

Glutathione transferases (GSTs) are a family of phase II detoxification enzymes that play a crucial role in the metabolism and detoxification of endogenous and exogenous compounds. This review article provides a comprehensive overview of human glutathione transferases, focusing on their structural features, enzymatic activities, expression patterns, and their significance in various cellular processes, including detoxification, antioxidant defense, and signal transduction. Moreover, we discuss the involvement of GSTs in human health and disease, including their associations with cancer, neurodegenerative disorders, drug resistance, and environmental toxicities.

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Received: 30-Jun-2023, Manuscript No. FMBP-23-108069; **Editor assigned:** 03-Jul-2023, PreQC No. FMBP-23-108069 (PQ); **Reviewed:** 17-Jul-2023, QC No FMBP-23-108069; **Revised:** 21-Jul-2023, Manuscript No. FMBP-23-108069 (R); **Published:** 28-Jul-2023, DOI: 10.37532/2048-9145.2023.11(4).89-91

Introduction

Glutathione transferase has a key function in cellular detoxification against xenobiotics and toxic chemicals, as well as against oxidative stress. Cancer cells, on the other hand, use this characteristic to gain drug resistance and enhance their survival. As a result, members of the family were discovered to be overexpressed in a variety of malignancies. Furthermore, various GST polymorphisms, spanning from null phenotypes to point mutations, were shown to correspond with the emergence of neuro-degenerative disorders in members of the family. A considerable lot of research has been conducted in recent decades to understand the role of GSTs in drug resistance, to create inhibitors to block this activity, and to utilize GSTs for prodrug specific activation in cancer cells [1-5].

Glutathione transferases (GSTs), also known as glutathione S-transferases, are members of the supergene family of phase II detoxifying enzymes found in practically all cellular life forms. GSTs are categorized into three primary protein families based on their subcellular distribution: Cytosolic, Mitochondrial or Kappa, and Microsomal (also known as Membrane-Associated Proteins in Eicosanoid and Glutathione (MAPEG)). The cytosolic GSTs are the largest family and are classified into seven distinct classes based on amino acid sequence and other structural similarities, which are represented by Greek letter names with alphanumeric letter designations, namely alpha (A), mu (M), omega (O), pi (P), sigma (S), theta (T), and zeta (Z). Cytosolic GSTs vary structurally from mitochondrial and microsomal enzymes in that they are made up of two subunits (25 kDa each), which can be homo-dimers of a single gene product or heterodimers produced by a separate gene. Each dimeric isozyme subunit has two functional domains: the N-terminal domain, which contains catalytically active cysteine, serine, or tyrosine residues, and the C-terminal domain. Each subunit has two substrate binding sites: the GSH binding site or G-site and an adjacent H-site for binding structurally varied hydrophobic xenobiotics or oxidative stress products. GSTs, the primary phase II detoxification enzymes, protect live cells by catalyzing the conjugation of glutathione (GSH) to a wide range of endogenous and foreign electrophilic compounds. GSH is a tripeptide (-l-glutamyl-l-cysteinyl glycine) that is generated in every cell's cytoplasm via a two-step ATP-requiring enzymatic process catalyzed by glutamate-cysteine ligase and glutathione synthase enzymes. GST tissue distribution and expression levels differ by class. The tissue distribution of soluble GSTs is summarized in a recent study. The disparities in GST tissue distribution imply that separate human tissues may detoxify or otherwise manage xenobiotics and/or medicines in different ways. Furthermore, certain chemicals, particularly those found naturally in fruits and cruciferous vegetables, can function as inducers of GST genes

via a variety of responsive elements, and such inductions are part of GST's adaptive response mechanisms to electrophilic chemical injury [6-10].

Glutathione transferases (GSTs) constitute a diverse superfamily of enzymes that catalyze the conjugation of glutathione (GSH) to a wide range of electrophilic compounds. In humans, GSTs are encoded by multiple gene families, and their expression varies across tissues, developmental stages, and under different environmental conditions. This introductory section provides a brief overview of the importance of GSTs in cellular homeostasis and the rationale for studying their role in health and disease.

Structure and Classification of Human GSTs

This section describes the structural features of human GSTs, including their subunit composition and the different classes they belong to. The human GSTs are categorized into several classes (Alpha, Mu, Pi, Theta, Omega, and others) based on sequence homology and substrate specificity. The discussion includes insights into the functional domains of these enzymes and their unique structural characteristics.

Enzymatic activities and substrates

Here, we delve into the catalytic functions of human GSTs. The article outlines the conjugation reactions catalyzed by these enzymes, wherein GSH acts as a nucleophile to neutralize harmful electrophilic compounds, such as reactive oxygen species (ROS), carcinogens, drugs, and environmental toxins. The section also highlights specific substrates for each GST class and how their activities contribute to cellular detoxification and protection against oxidative stress.

Regulation of GST expression

This section explores the factors influencing the expression of human GSTs. The regulation of GST genes can be modulated by various transcription factors and signaling pathways in response to cellular stress, exposure to xenobiotics, and during normal development. Understanding the regulatory mechanisms of GST expression is crucial to elucidate their role in different physiological and pathological conditions.

GSTs in health

This part of the review covers the physiological functions of GSTs in maintaining cellular redox balance and detoxifying harmful compounds. It discusses their roles in protecting against oxidative damage, inflammation, and various diseases. Additionally, GST polymorphisms and their associations with individual susceptibility to certain diseases are highlighted.

GSTs in disease

The focus of this section is on the involvement of GSTs in various human diseases. It discusses how alterations in GST expression and activity contribute to disease development and progression. Specific emphasis is given to cancer, neurodegenerative disorders (e.g., Alzheimer's and Parkinson's diseases), drug resistance, and their role in response to environmental toxicants.

Therapeutic implications

This section explores the potential of targeting GSTs as therapeutic agents or biomarkers in the context of various diseases. It discusses current research on GST inhibitors and activators and how manipulating their expression and activity could be utilized for therapeutic interventions.

Conclusion

The review concludes with a summary of the key findings on human GSTs and their importance in maintaining cellular homeostasis and protecting against various diseases. It emphasizes the potential for further research in this area and how a deeper understanding of GSTs could lead to novel therapeutic approaches and diagnostic strategies. Overall, this review article provides a comprehensive and up-to-date understanding of human glutathione transferases, shedding light on their multifaceted roles in health and disease. It serves as a valuable resource for researchers, clinicians, and students interested in exploring the diverse functions of GSTs in human biology.

Recent discoveries in this research have underlined the significance of GST activities and the function that these enzymes play in a variety of cellular processes, as well as in conferring chemotherapy resistance. It is not unexpected, in this background, that a large number of inhibitors and pro-drugs targeting GSTs have been synthesized and tested thus far, with new scaffolds or analogues being published every year. Some of these compounds have also entered clinical studies, and we may see the approval of a GST inhibitor or pro-drug for patient therapy in the future. While reviewing the literature for this work, we noted and reported an increased interest in the function that GSTs play in

neurodegeneration, where isozymes from the family may be up-regulated, mutated, or absent depending on the illness. Research in this area is very active, with the potential to identify specific GSTs or specific GST polymorphic forms as potential pharmaceutical targets.

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