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Complex Role of Glutathione S-Transferases in Cancer

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Introduction

The majority of living things have cytosolic Glutathione S-transferase (GST) isozymes, which were first discovered in rat liver in the early 1960s. Since then, GSTs have drawn a lot of study interest due to their numerous functions, including the detoxification of reactive electrophiles, cell signalling, anti-apoptotic activity and pro- and anti-inflammatory responses. According to their subcellular location, the GST enzymes are classified into three types: membrane-bound microsomal, mitochondrial and cytoplasmic. The scientific community is currently preparing to use novel methodologies to evaluate the association between GSTs and cancer risk or progression, which may ultimately present novel and exciting options for target discovery and therapeutic development. In this review, we provide a brief overview of the composition and functioning of mammalian GSTs.

Description

The largest and most diverse group of GSTs is the cytosolic enzymes found in humans. There are at least eight different isoenzymes that make up these phase II detoxification enzymes: Alpha (A), Kappa (K), Mu (M), Omega (O), Pi (P), Sigma (S), Theta (T) and Zeta (T) (Z). The four distinct classes of this superfamily, beta, delta, phi and tau, are also found in bacteria, insects and plants. Members of the GST family have been the subject of numerous studies and it is evident that these molecules have advanced considerably [1,2]. Researchers are now urged to consider GSTs in ways other than their conventional role in drug detoxification as a result.

Every organ has a distinct GST profile because different GST genes appear to express differently in various tissues and cell types. It was noticed that while GSTP1 is more abundant in extrahepatic tissues, GSTA1 expression is highest in the liver, kidney and testicles. GSTT1 is expressed predominantly in kidneys and liver. GSTP1 generally seems to be expressed more strongly in proliferating cells than in differentiated cells. Chromosome 6p has a group of five GSTA (or alpha) genes, Chromosome 1p has a group of five GSTM (or mu) genes, Chromosome 10q has two GST-omega genes, Chromosome 11q has two GST-theta genes and Chromosome 14q has one GSTZ1 gene. Within the collection of functional genes, pseudogenes are frequently located in various chromosomal regions [3].

The light scattering results from the subsequent study of GSTP's interaction with 1-Cys peroxiredoxin confirmed that the active complex is a heterodimer made up of equimolar quantities of two proteins. This work also demonstrated that, in the presence of potassium bromate, GSTP is dissociated to monomer while maintaining its catalytic activity [4].

It has been shown that the dimermonomer equilibrium shifts toward the monomer by eliminating the charges at the subunit interface of GSTP, namely Arg70, Arg-74, Asp-90, or Asp-94 [5]. Additionally, it was shown that the monomer of GSTP maintains its catalytic activity because to the predominance of GSH and electrophilic substrate sites inside each subunit.

Furthermore, it was shown that Tyr-198 phosphorylation at the C-terminal region of GSTP by EGFR causes the dimer-monomer equilibrium of GSTP to shift to the monomeric form, where it binds to JNKs and inhibits downstream signaling. Together, these results show that there is still disagreement on the dimer-monomer transition of GSTs. However, several real-world examples of monomeric GSTP interacting with other proteins provide compelling evidence that monomeric GSTs are real and capable of catalysis.

Water, electrolyte and waste excretion are all regulated by the kidneys. Additionally, they support red blood cell production, bone calcification and systemic blood pressure (BP). The kidney has its own autocrine and paracrine signalling pathways in addition to responding to external hormonal cues. Depending on the disease, these signalling pathways may be maladaptive or adaptive during normal physiological function. To respond to physiologic and pathophysiological changes, they facilitate communication among podocytes, vascular endothelium, stroma and epithelial cells at various levels of the nephron [2]. With a focus on recent developments, this article reviews our current understanding of the signalling mechanisms among tubular, interstitial, vascular and glomerular cells. We'll talk about the importance of these systems for treatment, disease and health [6].

The kidney contains ETA and ETB, two groups of recognised endothelin receptors. Both are expressed in the inner medullary collecting duct, enabling these cells to engage in autocrine and paracrine signalling. When osmotic water permeability is induced by increased arginine vasopressin (AVP), ET-1 and its receptors provide negative feedback control. Both collecting ducts and thick ascending limbs (TALs) contain ETB receptors and when these receptors are stimulated by ET-1, nitric oxide synthase is stimulated and NaCl transport is inhibited (NOS). Nitric oxide production is increased and this reduces the activity of epithelial sodium channels (ENaC) and Na+K+-ATPase in the collecting ducts and distal convoluted tubules.

Elevated urinary albumin excretion, reduced glomerular filtration rate (GFR) and progressive decline in kidney function, which ultimately results in end-stage kidney failure, are clinical features of DN. The pathogenesis of DN is primarily influenced by changes in intracellular metabolism brought on by hyperglycemia, such as the buildup of advanced glycation end products (AGEs), activation of protein kinase C and oxidative stress. The polyol pathway's increased glucose flux is a major contributor to oxidative stress. The diacylglycerol (DAG)-PKC pathway is also activated by chronic hyperglycemia and it plays a role in the control of vascular permeability, vasoconstriction, ECM synthesis and turnover, cell growth, angiogenesis, cytokine activation and leukocyte adhesion [7].

Conclusion

It is clear that the significance of GSTs, in particular GSTP, in the emergence of cancer is growing. The overexpression of GSTP found in many chemoresistant cancer types has contributed to the link between GSTP and cancer. However, from a functional standpoint, it was discovered that most anticancer medications are poor substrates for GSTP1 and have weaker catalytic constants for GSTP1 conjugation reactions. As a result, attention has shifted to GSTP's involvement in a number of cellular functions, especially in the regulation of various kinases and the post-translational process of S-glutathionylation of a number of proteins.

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Conflict of interest

There are no conflicts of interest by author.

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