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Glutathione S-transferases' Complex Function in Cancer

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Introduction

Most forms of life contain cytosolic Glutathione S-transferase (GST) isozymes, which were first identified in the early 1960s in rat liver. Due to its several functions, such as the detoxification of reactive electrophiles, cell signalling, anti-apoptotic activity, and pro- and anti-inflammatory responses, GSTs have since attracted a lot of study interest. The GST enzymes are divided into three types according to their subcellular location, including membrane-bound microsomal, mitochondrial, and cytoplasmic. In order to assess the relationship between GSTs and cancer risk or advancement, the scientific community is now preparing to use fresh methodologies, which may ultimately present new and exciting options for target discovery and therapeutic development. We briefly discuss the structure and operation of mammalian GSTs in this review, as well as their complex role in cancer.

Description

The cytosolic enzymes found in humans make up the largest and most diversified group of GSTs. Alpha (A), Kappa (K), Mu (M), Omega (O), Pi (P), Sigma (S), Theta (T), and Zeta (T) are at least eight kinds of isoenzymes that make up these phase II detoxification enzymes (Z). In addition, bacteria, insects, and plants all contain members of the four separate classes of this superfamily, known as beta, delta, phi, and tau. Numerous studies have been done on members of the GST family up to this point, and it has become clear that these molecules have come a long way [1,2]. As a result, researchers are now encouraged to think of GSTs in ways other than their traditional function in drug detoxification.

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.

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.

Conflict of Interest

There are no conflicts of interest by author.

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