Mini Review

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Glutathione s-transferases detoxify endogenous and exogenous toxic agents-mini review

Abstract

Glutathione S-transferases (GSTs) are belongs to phage II detoxification enzymes which play an important role in detoxification/biotransformation of endogenous and exogenous toxic agents like reactive oxygen species (ROS), reactive nitrogen species (RNS) and xenobiotic including environmental carcinogens. The generation of reactive oxygen/nitrogen species is known as oxidative stress which causes molecular damage. Oxidation of proteins leads to loss of certain function. Oxidation of lipids causes the disruption of biological membrane. That the DNA mutation and oxidative DNA lesions which are critical in carcinogenesis. This mini review discussed about the detoxification role of GSTs against endogenous and exogenous toxic compounds.

Keywords: glutathione s-transferases, endogenous & exogenous toxic agents, molecular damage

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Abbreviations: GST, glutathione s-transferases; ROS, reactive oxygen species; RNS, reactive nitrogen species: GSH, glutathione

Introduction

The biotransformation of foreign substances (xenobiotic) including drugs in the body is divided into phase I, II and III. But phase II enzymes are playing a key role in the biotransformation of endogenous compounds and xenobiotics to easily excretable forms and also the metabolic inactivation of pharmacologically active substances. The phase II enzymes can perform biotransformation through conjugation reactions. Glutathione S-transferases (GSTs) are one of the versatile detoxification enzymes among phase II enzymes, which are involved in the xenobiotic metabolism and play major role in cellular protection against oxidative stress. GSTs (EC. 2.5.2.18) are belongs to a family of multifunctional enzymes which conjugate electrophilic intermediates with the endogenous tripeptide glutathione (GSH).[1] GSTs are ubiquitous, multitalented enzymes which catalyse the nucleophilic addition of the glutathione (Glu-Cys-Gly) to numerous hazardous xenobiotic including phase I electrophilic and carcinogenic metabolites.[2] There are cytosolic, mitochondrial and membrane associated GSTs, but detoxification is the key function of cytosolic GSTs.[1] Mammalian cytosolic GSTs are extensively studied.[3]

Molecular degeneration

The oxidative stress arises from an imbalance between oxidants and antioxidant enzymatic system. Which causes the oxidation of biomolecules with consequent loss of biological functions of them and it leads to potential oxidative damage to cells and tissues. The accumulation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) shows numerous deleterious effects such as lipid peroxidation; protein oxidation and DNA damage.[4]

Disruption of lipids

That the lipid peroxidation occurs in two forms in the biological system, the participation of cyclooxygenase and lipoxygenase in the oxidation of fatty acids known as enzymatic lipid peroxidation, participation of transition metal, the ROS, RNS in the fatty acid oxidation, called as non-enzymatic lipid peroxidation.[5] The lipid peroxidation disrupts the normal structure and function of lipid bilayers of membrane which surrounding both cell and organelles. That the lipid peroxidation which can alter membrane permeability, transportation and fluidity.[6]

Oxidation of proteins

Carbonyl derivatives of certain amino acids like proline, lysine, arginine and threonine oxidation are used as markers for oxidative stress. That the oxidation of aromatic amino acids like tyrosine, various products are formed due to interaction either ROS (di-tyrosine) or RNS (3-nitrotyrosine).[7] That the modified proteins by oxidation are usually recognized and degraded in the cells, but some oxidized proteins are accumulate over time and lead to cellular dysfunction. That the lipofuscin which is a brown-yellow pigment, it is a product of iron-catalysed oxidation (polymeerization) of proteins and lipids, which is extremely resistant to proteolysis, it accumulates and which is used as an aging marker.[8]

Oxidation of nucleic acids

Oxidative stress can lead to different lesions in DNA which are direct modification of bases of nucleotides including single and double strands breaks. Among all the bases of the nucleotides, guanine is most susceptible to oxidative changes, due to its lower reduction potential and hydroxyl radicals interact with imidazole ring of this nitrogenous base.[9] The well-studied marker for oxidation of DNA is 8-hydroxydeoxyguanosine which is a product of guanosine oxidation by $HO^{\bullet}$.[7,10] this product can pair with adenine and generate a GC/TA mutation upon replication.[10] The most relevant marker is the homologue 8-hydroxyguanosine for RNA oxidation. The RNA if more frequently oxidized than DNA, because of its closer localization to ROS and RNS occurrence in cell. That the major consequences of RNA oxidation which are the breakage of strand and ribosomal dysfunction, preventing correct protein production.[7]

Detoxification of exogenous hazardous agents

Glutathione S-transferases (GSTs) are detoxifying a large number of exogenous toxic agents like carcinogens, drugs and environmental pollutants. The chemotherapeutic agents of cancer such as adriamycin, 1, 3-bis (2-chloroethyl)-1-nitrosourea (BCNU), busulfan, carmustine, chlorambucil, cis-platin, crotonyloxymethyl-2-cyclohexenone (COMC-6), melphalan, mitozantrone, thiotepa, cyclophosphamide and ethacrynic acid are detoxified by GSTs.[11] Environmental chemicals and their metabolites like acrolein, atrazine, DDT, inorganic arsenic, lindane, Malathion, methyl parathion, muconaldehyde and tridiphane are detoxified by GST isoenzymes.[12,13] A large number of epoxides like fosfomycin and those derived from environmental carcinogens, polycyclic aromatic hydrocarbons (PAHs) are detoxified by GST. Activated metabolites N-aacetoxy-PhIP of heterocyclic amine, 2-amino-1-methyl-6-phennylimidazo [4, 5-b] pyridine (PhIP) which produced by cooking protein-rich food is also detoxified by cytosolic GST.

Activation of xenobiotics

The conjugation reaction catalysed by GST can form less reactive and readily excreted products. But in some cases that the glutathione (GSH) conjugate is more reactive than the parent compound like short chain alkyl halides that contain two functional groups and 1, 2-dihaloethanes, where the GSH conjugate rearranges to form an episulfonium intermediate which responsible for DNA modification.[14] The conjugation of GSH with the solvent dichloromethane facilitate formation of the highly unstable Schloromethlglutathione which capable to modify DNA.[14,15]

That the moderately toxic compounds like allyl-, benzyl-, phenethyl-isothiocyanates and sulforaphane are reversibly conjugated with GSH by GST to form thiocarbamates which spontaneously degrade to their isothiocyanates by releasing GSH. Again that the isothiocyanates may be taken up by the cell and re-conjugated with GSH and then form thiocarbamate and then revert to the isothiocyanate. Due to this cyclic process, intracellular GSH levels are decreased and facilitate the distribution of isothiocyanates entire the body. Such isothiocyanate either low GSH content or not conjugated with GSH, but rather are more likely to thiocarbalate proteins, which result in cell death.[16]

Detoxification of endogenous hazardous agents

The GSTs are exhibits moderate role in lipid peroxidation in biological membranes known as non-selenium glutathione peroxidase (GPx) activity. The non-selenium (GPx) shows activity with 1-palmitoyl-2-(13-hydroperoxy-cic-9, trans-11-octadecadienoyl)-L-3-phosphadylcholine, phospatidylcholinehydroperoxide and reducing lipid hydroperoxides which are in membranes.[17–19]

The transferases can reduce cholesterylhydroperoxides,[20] fatty acid hydroperoxides, (S)-9-hydroproxy-10, 12-octodecadieonic acid and (S)-13-hydroperoxy-9, 11-octadecadieonic acid.[21] That the lipid peroxidation end products like 2-alkenals acrolein, crotonaldedyde and 4-hydroxy-2-alkenals are conjugate with GSH by GSTs.[21] GSTs catalyze the GSH conjugation with cholesterol-5, 6-oxide, epoxyeicosatrienoic acid and 9, 10-epoxystearic acid, which indicating its role in cellular protection against oxidative stress by harmful electrophiles.[1]

Conclusion

Both endogenous and exogenous toxic agents are exhibiting numerous deleterious effects on biological system. Theses toxic agents have impact on molecular damage. However, the biological system has been developed an efficient antioxidant enzymatic system. GSTs are multifunctional antioxidant enzymes which have non selenium glutathione (GSH) peroxidase (GPx) activity in addition to GSH transferase activity. By these two activities, GSTs detoxifying wide range of hazardous substances.

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Conflict of interest

Authors do not have any potential conflict of interest.

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