Biosynthesis, metabolism, and utilization

Different ways glutathione acts to protect mammalian organisms from potentially toxic exogenous and endogenous compounds.

Glutathione (GSH or gamma-glutamylcysteinylglycine) is a tripeptide and a sulfhydryl (thiol or -SH) antioxidant, enzyme cofactor and antitoxin that is made up of three amino acids namely L-glutamine, L-cysteine and glycine. The water solubility nature make it to be found in the cell cytosol and within aqueous phases of living system, although is constantly encountered in animals, plants and microorganisms (Kosower NS et al 1978 , Meister A et al 1976, Kidd PM et al 1991 and Lomaestro BM et al, 1995). Glutathione exists intracellularly in two forms in either reduced form or oxidized form which can be an antioxidant in reduced form (GSH) and sulphur-sulphur bond compound called glutathione disulphide (GSSG) in the oxidized form. Sensitive indicator of oxidative stress is the ratio of the reduced form (GSH)/ oxidized form (GSSG) which is also important in cell functioning in the organisms.

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The homeostatical control status of glutathione by continuous self adjusting to equilibrate GSH production, its reprocessing from GSSG and its usage is a function of enzymes such as GSH synthetase, GSH reductase, peroxidises, transferases, transhydrogenases and transpeptidases. Cysteinyl moiety is the functional element of glutathione that provides the thiol reactive group which is liable for the sustenance of protein structure and functions through proteins disulfide linkages reduction, controlling of production and breakdown of protein, sustenance of immune function, defence against oxidative injury, removal of reactive chemicals. The metabolism and function

of glutathione is directly decided by structural elements of glutathione which are γ-carboxyl peptide linkages of glutamate and C-terminal glycine presence. All mammalian cells produces GSH (Meister and Tate, 1976) and major site of biosynthesis is the liver (Deleve and Kaplowitz, 1991). The production of GSH occurs in the cytosol of cell and its breakdown takes place outside the cell; production involves a two phase reaction catalyzed by GSH synthetase and γ-glutamylcysteine synthetase that uses two moles of adenosine triphosphate(ATP) per one mole of GSH while the breakdown are catalyzed by γ-glutamyl transpeptidase and dipeptidases present on the top surface of epithelial tissues. The first phase is under the influence negative feedback from its end product, GSH (Richman and Meister, 1975). The blockage of the regulatory site of the enzymes by excess glutamate can partially prevent feedback inhibition (Meister, 1984; Meister and Anderson, 1983; Richman and Meister, 1975). The limiting factor after the utilization of GSH and loss of feedback inhibition is the availability of cysteine. The breakdown products of GSH S-conjugates and GSH are the same (glutamate, glycine, and cysteine) and are also metabolized by same degradative enzymes which metabolized GSH and the products can be reabsorbed into the cell for GSH production. Intracellular N-acetyltransferases can acetylate cysteine S-conjugates on the amino group of residue of cysteinyl to form mercapturic acids (N-acetylcysteine S-conjugates) which are released into the circulation or bile (Hinchman et al., 1991). γ-glutamyl cyclotransferase is responsible for the change of excess γ-glutamylcysteine accumulation, in the absence of its change to GSH which can result to 5-oxoproline and 5-oxoproline accumulation has harmful effect because of metabolic acidosis.

REDOX AND CELLULAR REGULATORY ROLE OF GSH

GSH Peroxidases and phospholipid hydroperoxide GSH peroxidases are antioxidant enzymes which uses glutathione has an important cofactor although GSH peroxidases exist in both selenium-dependent and non-dependent forms (Zhang L., 1989). GSH peroxidases acts by reacting hydrogen peroxide and other peroxides with GSH in water phase to detoxify them while peroxides produced in cell membranes and lipophilic cell phase are detoxified by phospholipid hydroperoxide GSH peroxidases using GSH (Cathcart RF III., 1985). GSH can also be used by GSH transhydrogenases as a cofactor in the reconversion of dehydroascorbate to ascorbate, ribonucleotides to deoxyribonucleotides and interconversion occurring between disulphide and thiol group. GSH reducing power source is the nicotinamide adenine dinucleotide phosphate(NADPH) in reduced form which is from the pentose phosphate shunt that glutathione reductase uses as a source of electron in the reprocessing of GSSG to GSH (Cathcart RF III., 1985) and indicative of increased risk of oxidative injury in subjects unable to produce enough NADPH due to GSH insufficiency. Vitamin E and carotenoids which are lipid-phase antioxidant can be conserved by GSH reducing power ability (Meister A et al, 1994). There are two pools of GSH in liver which are the cytosolic GSH and mitochondrial GSH; the first has a half-life of 2-4 hours and the second half-life is about 30hours (Meister A et al, 1995). There are various disorders associated with two enzymes involved in the two phase synthesis of GSH which include peripheral neuropathy, haemolytic anaemia, aminoaciduria, CNS function defects, myopathy, spinocerebellar degeneration in inherited deficiency individuals (Meister A, Larsson A., 1995). Kosower NS. et al,. 1978 discovered the essential role of GSH in cellular

homeostasis and various cellular functions; biological processes such as cell maturation, protein synthesis, transmembrane transport, intermediary metabolism, enzyme catalysis and receptor action. Ondarza RN. , 1989 also observed that redox uniqueness are essential to life process with many vital enzymes and about eight taking part in glucose metabolism being regulated by redox balance (2 thiol group and disulphide). Intracellular sulfhydryl (-SH) groups of proteins are mainly pro-homeostatically regulated by GSH (Crane FL. et al,. 1988). The whole range of biomolecules are protected by combination of the reducing power of glutathione with other antioxidants and ascorbate, which also helps in regulating their function, and to assist the survival and maximum functioning of the cell as a living unit.

Metallothioneins are proteins which can bind with heavy metals and potential sulfhydryl poisons due to glutathione’s reducing power and its -SH character that set the redox stage and also speed up their removal from the body later (Hidalgo J. et al,. 1990). The redox state of many cellular environments are ” fine- tune” homeostatically by glutathione reducing power. GSH plays a central role in the antioxidant defense system that protects against various free radicals and oxidative stressors which it’s exposed to regularly (Cross CE, Halliwell B, Borish ET, et al. 1987). The exogenous oxidative insults tends to be more easily controlled by GSH.

SYSTEMIC ANTITOXIN ROLE OF GSH

Organs like lungs, intestines, kidneys and liver which are directly exposed to exogenous toxins are often important to GSH, although high concentration of GSH in lower section of lungs helps neutralize inhaled toxins (cigarette smoke) and free radicals made by activated lung phagocytes (Lomaestro BM

et al, 1995; Cross CE, Halliwell B, Borish ET, et al, 1987). The detoxification of substances foreign to body is mainly by the liver and also carries GSH to other organs. The activity of GSH transferase enzymes (GSTs) drains GSH in normal functioning liver while malnutrition or starvation depletes liver GSH stores (Deleve LD, Kaplowitz N. 1990; Mandl J, et al,. 1995). The electron-donating co-factor of GSTs is GSH due to definite specificity it's has for it, although GSTs have fairly wide specificity for their substrates. GSH plays a fair considerable role in liver P450 conjugation activity which is responsible for about 60% of liver metabolites present in bile but GSH conjugation is certainly of full advantage to organism though it is not positive in every circumstance. There are different classes of xenobiotics that induce P450 enzymes which produce more toxic GSH conjugates than the parent xenobiotics (Monks TJ, et al,. 1994). Depletion of liver pool of GSH can decrease conjugation and increase xenobiotics toxicity for example are Tylenol® (experimental acetaminophen) and bromobenzene toxicity (Kidd PM. 1985). Glutathione and also glutathione S-transferase plays important role in the regulation of both acute and chronic chemical toxicity in the lung (west et al., 2003). Detoxification function of glutathione is dependent on the ability of its synthesis in the lungs and the cellular localization (plopper et al., 2001b, West et al., 2000). In human liver, the pulmonary glutathione S-transferase activity is about 30% while in the rodents liver, it is 5-15% (Buckpitt and Cruikshank, 1997). The distribution of isoforms of glutathione S-transferase varies in the lungs. The result of polymorphisms expression in humans and potential for similarity of this with cancer of the lungs, particularly in smokers, makes glutathione transferase a focus point of acute interest. There are equilibrium systems working between enzymes, that is a

decrease in one enzymes can cause an increase in another enzymes at the same time; the location and balance of all the enzymes determines toxicity.

CONCLUSION

Glutathione functions in the body are numerous which include neutralization of free radicals and reactive oxygen compounds, sustaining exogenous antioxidant in their reduced forms (Vitamins E and C). It also plays important role in diverse metabolic and biochemical reactions for example enzymes activation, DNA synthesis and repair, amino acid transport, protein synthesis, prostaglandin synthesis etc. In the immune system, glutathione manifest full potential by adjusting antigen being presented to lymphocytes which might influence formation of cytokine, resulting in formation of cellular or humoral responses, magnitude of responses are increased by promoting lymphocytes production, thereby causing promotion of killing activity of cytotoxic T cells and NK cells and regulating apoptosis; thus sustaining control of immune system.

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