Progress on Bioselenium Researches

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Abstract. For the past few years, selenium has permeated various fields in the life science with its strong vitality, and this fields expanded rapidly. In this paper, research progress on macromolecular bioselenium, especially on selenoproteins, selenium-nucleic acids and the selenium polysaccharides were summarized. Based on this, prospects on the research direction of bioselenium were discussed.

1. Introduction

Selenium exist in organism mainly in organic forms. It is so important to our human health that many specialists and scholars are inspired to spare no efforts trying to figure out its existent forms, biological functions and metabolism in organism deeply and comprehensively. The discovery of glutathione peroxidase (GPx) laid a foundation to establish the selenium biochemistry, after that, more and more biological functions of selenium were discovered and its research field became larger and larger.

2. Main forms of bioselenium

There are mainly two kinds of bioselenium in organism [1], the micromolecular and the macromolecular, which are separately represented by selenoamino acids and selenoproteins. The selenocysteine (SeCys) and selenomethionine (SeMet) are the major selenoamino acids and the GPx is the major selenoprotein. The main forms of bioselenium were listed below.

Table 1. Main forms of bioselenium

	animal	plant	microorganism
micromolecular bioselenium	SeCys, SeMet, dimethylselenide, dimethyldiselenide, trimethylselenonium,selenotaurine,	SeCys, SeMet, elemental selenium, selenohomocysteine, selenocystathionine, dimethyldiselenide Se-methylselenocysteine, Se-methylselenomethionine, dimethylselenide, selenocystine	SeCys, SeMet, dimethyldiselenide, elemental selenium, dimethylselenide
macromolecular bioselenium	selenoproteins, selenium-nucleic acid	Se-polysaccharide, selenoproteins, selenium-nucleic acid	Se-polysaccharide, selenoproteins, selenium-nucleic acid

3. Selenoprotein

Selenoproteins are the major forms of bioselenium in organism. SeCys and SeMet are the only two kinds of selenoamino acids that are covalently bonded in proteins. Thereinto, the SeCys is the 21st

amino acid in protein molecules which is synthesized by organisms [2]. At present, in-depth studies on selenoproteins of animals have been done at home and abroad. But for the 25 kinds of selenoproteins founded in our human genome, only the GPx and a few other kinds of them were well understood by us. Therefore, taking the GPx, iodothyronine deiodinase (ID), thioredoxin reductase (TrxR) and Selenoprotein P (Sel P) for examples, research progress of the selenoprotein were summarized below.

3.1 Glutathione Peroxidase (GPx)

GPx was first founded by Mills in 1957 and its relationship with selenium was confirmed by Flohé's and Rotruck's research groups [3]. It was the first selenoenzyme founded in mammals. Its four main types are GPx-1 (cellular type), GPx-2 (gastrointestinal type),GPx-3 (serous type) and GPx-4 (phospholipids hydrogen peroxide type).

Eliminating the lipid hydroperoxides was the principal function of GPx, and it played an important role in anti-aging for it could slow down the cell's senescence, which was caused by the lipid hydroperoxides [4]. Arthur et al [5] found the GPx could catalyze the glutathione into oxidized glutathione so that the poisonous peroxides would be changed into innoxious hydroxy compounds. It also could protect cytolemma's structure and function from peroxides by accelerating its decomposition. After genomes of the arabidopsis were analyzed, 7 GPx genes were founded by Milla et al [6]. Their research showed these genes could react to several different abiotic stress, such as oxidative stress. Moreover, Bierl C's research [7] indicated that, in the GPx-3 gene promoter's region of human, there existed an oxidation reaction element (ARE) and a metal reaction element (MRE). This two elements were sensitive to active oxygen and antioxidants, and they could effect the transcription of the GPx-3 gene. In addition, according to their investigations, Hao Ying et al [8] also confirmed the GPx-3 gene had influences on the incidence of hypertension disease.

3.2 Iodothyronine Deiodinase (ID)

IDs exist in plasma membranes with three types including D1 (iodothyronine deiodinase,type 1), D2(iodothyronine deiodinase,type 2) and D3 (iodothyronine deiodinase,type 3) [9]. As a main secreta of the thyroid, T_4 (3,5,3',5'-triiodothyronine) wouldn't have an enzymatic activity until it turned into the T_3 (3,5,3'-triiodothyronine) by the ID's catalysis, and this was a mode on which organisms relied to adjust their iodine content. Researches of Ferreiro et al [10] indicated that, ID was needed to maintain the content and function of the thyroxine in brain tissues. D2 and D3 were the primary ID in central nervous system, and they were independent to thyroxine's content in circulatory system. Organism could adjust the content of thyroxine according to their physiological status and critical time in regional tissues, hence, the D2 and the D3 played a key role in the signal path of the thyroxine .

Now, researches about the ID are mainly focused on the gene's expression in mammals' embryo tissues, such as brain and central nervous system during their development process [11]. By studying the exogenous T3's effects on activities of duck embryo liver cells and expressions of D3 mRNA, Wen-Qiang SUN et al [12] founded that the exogenous T_3 could promote the growth of duck embryo liver cells, and D3 might play a positive role in the proliferation of liver cells. Besides, results of Tian-Tian LIU et al [13] showed, expressions of D2 in brain tissues of premature rabbit with germinal matrix-intraventricular hemorrhage (GM-IVH) increased while the expression of D3 decreased in some extent after thyroxine intervention. Their results indicated that, by stimulating other neurotrophic factors' secretion, T_3 had an effect on neurocytes in a degree and could mitigate the GM-IVH's effects on the ID's expression .

3.3 Thioredoxin Reductase (TrxR)

It was Tamura and Stadtman who first confirmed the TrxR was a kind of selenoenzyme in higher eukaryotic cells [14]. The thioredoxin (Trx), NADPH and this enzyme together constituted a thioredoxin system [15]. TrxR with an extensive substrate specificity was very important in adjusting several physiological processes, such as the redox and the growth of cells [16]. In addition, the TrxR was closely related to the pathogenesis of some disease, like cancers, cardiovascular disease,

autoimmune defects, central lesion and so on [17]. Nalvarte et al [18] researches showed that functions of cell were influenced by the different activity of TrxR. TrxR with high activity could promote the cells' division while cells' apoptosis were also promoted when TrxR's activity was low. Similar results were also confirmed by Mahamood et al [19]. Their results indicated, the myocardial cells' division increased when the TrxR's expression was low while its apoptosis could be inhibited by the TrxR's overexpression.

3.4 Selenoprotein P (Sel P)

Sel P, a kind of plasmic selenoprotein, has been studied extensively in recent years. It was Herrman who first discovered this selenoprotein from rats plasma by SDS-PAGE in 1977 and revealed its molecular weight was 49 kDa. After that, this selenoprotein was confirmed by Burk et al with 75Se isotope labelling method. Motsenbocher and Tappel also isolated the protein in the same year and named it Sel P, and they founded selenium existed in the Sel P in the form of SeCys [20].

Sel P was a kind of extracellular glycoprotein which was the main form of plasma selenium [21]. Now, the preliminary findings suggested the Sel P played an important role in maintaining selenic dynamic equilibrium and adjusting selenic content in organism, and it was closely related to sperm production, brain damage and parasitic infection [22]. Hill et al [23] researches showed the Sel P was synthesized by hepatocyte and transported in plasma to ensure the selenic content balance in different organs. In this way, the organism could keep the balance between the selenic reservation and allocation in hepatic tissue. Misu et al [24] also verified the expression of Sel P was of great importance in glycometabolism and insulin resistance for it could reduce the insulin sensibility and glucose tolerance by inhibiting the AMPK's activity and insulin receptor's phosphorylation. Therefore, Sel p has played a critical role in diabetes mellitus type 2 which was caused by insulin resistance.

4. Selenium-Nucleic Acid

Selenium in tRNA of escherichia coli was first discovered by Sealinger et al [25] in 1972, however, this phenomenon was thought to be a result of the sulfur that was replaced by selenium randomly in tRNA. But in 1975, Frost founded selenouracil in tRNA. Besides, in 1981, Ching et al [26] founded the content of selenium in the Se-tRNA wouldn't decrease when the sulfur's concentration was very high. This means, that selenium entered into the tRNA wasn't random but intentional. In 1983, three fairly pure Se-tRNA were obtained from escherichia coli by Wittwer et al [27] and these Se-tRNA turned out to be an isoacceptor tRNA of lysine and glutamic acids. In the same year, Wittwer proved that selenium in tRNA of escherichia coli existed in the form of 5-methylamino-2-Se uracil (mnm^5Se^2U), thereby, the proof that selenium bonded in tRNA intentionally was founded. In addition to this, their research showed, compared with S-tRNA, Se-tRNA was more beneficial to the transcription of the lysine password (AAG) and the glutamate password (GAG), and it was critical important in adjusting the efficiency when mRNA of the AAG and GAG were translated into proteins.

Se-tRNA was a proof of how the selenoproteins were synthesized in organism.Its content was consistent with the selenoproteins' expression and the GPx's activity. When selenoproteins were synthesized, SeCys was transported in the form of Se-tRNA. Then, taking selenic phospholipid as selenium donor, selenium was combined with serines by the enzymatic action of an enzyme (selenophosphate synthetase, SPS), later, the serine was used as a carbon skeleton to synthesize the SeCys.

5. Selenium Polysaccharide (Se-polysaccharide)

It was confirmed that the natural Se-polysaccharides existed in various kinds of animals, microorganisms and especially plants [28]. Researches on the natural Se-polysaccharides were restricted in a degree for its content was really low in organism. Inorganic selenium was added into the culture mediums of fungus and algaes by people in a appropriate culture condition to obtain

Se-polysaccharides with the help of the creatures' enrichment and transformation properties [29]. Now, several kinds of natural Se-polysaccharides were successfully gained, such as ganoderma lucidum Se-polysaccharide, shii-take Se-polysaccharide, spirulina Se-polysaccharide and garlic Se-polysaccharide.

As researches of Se-polysaccharides revealed, they were mainly two types of monosaccharides, homogeneous and heterogeneous glycan, that formed the Se-polysaccharide. The heteroglycan was the major form of Se-polysaccharides which were usually composed by various kinds of monosaccharides such as galactose, glucose, rhamnose, xylose, fucose, mannose and so on, and those monosaccharides always existed in the Se-polysaccharide with the D-configuration. The 1-3 glycosidic bond formed the backbone of Se-polysaccharides while its branches were diverse. As a characteristic composition, SeH- and $R_1-\overset{O}{\overset{\|}{Se}}-O-R_2$ were the two possible forms of selenium that existed in Se-polysaccharides [30]. But more researches will still be needed to figure out the higher structure of most Se-polysaccharide.

Bioactivities of selenium and polysaccharide are combined together in Se-polysaccharide, and the Se-polysaccharide shows superior effects to their single operation. Therefore, Se-polysaccharides have a very high application value in medical science and clinical field. Studies have shown [31] ,Se-polysaccharide can enhance body's immunity by improving macrophage's phagocytosis, it can enhance body's antioxidant ability by eliminating the free radicals, it can inhibit viral infections by stopping the viral adsorption,it can reduce the heavy metal's toxicities by curbing the metal's accumulation in organism and it also can improve the insulin's sensibility by protecting islet cells so that it is beneficial for diabetes.

6. Prospect of the Bioselenium

Nowadays, importance of bioselenium to health has been deep-rooted in people's mind due to the large amounts of researches on it. Therefore, significance of exploitation and utilization on natural selenic resources have became so self-evident in the life science. There are all kinds of bioselenium in organism but some of its higher structure and action mechanism remained unknown to us. Thus, in order to figure out their accurate configurations and find out some low abundance bioselenium, high-efficiency separation and purification technologies are needed to obtain various high-purity bioselenium samples form different powerful selenium-rich artificial cultures. Besides, biological mechanism of the bioselenium is so complicated in organism that people have focused their attention not only on its antioxidation but also on its response to hormone. The relationship between bioselenium and illness involves lots of research area such as medicine, molecular biology, genomics, proteomics and so on. For this reason, some advanced technologies, such as ICP-MS, HPLC-ESL-MS/MS et al, will make a difference in exploring the vary kinds of bioselenium's mechanism in organism at the molecular level. All in all, massive work should be devoted to the bioselenium field all the time.

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