Selenium and Selenocompounds in Lymphoma

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Lymphomas have been increasing at an alarming rate globally and causing deaths worldwide due to the lack of effective therapies. Among different pharmacological agents, selenium (Se) and selenium-related compounds are widely tested and have gained interest as anticancer agents due to their selectivity to cancer and high efficacy for lymphoma treatment over recent decades. Se is a trace non-metallic element identified as an essential micronutrient that mediates a range of biological functions after incorporation into selenoproteins (SePs), and thus affects the overall quality of human health. Specifically, low levels of Se in serum have been linked with aberrant immune functions, cancer, inflammatory diseases, and predictive of worse outcomes in patients with hematological malignancies including lymphoma. Over the past, a number of promising selenium compounds (SeCs) have been developed to mimic and alter the functions of SePs to achieve pharmacological interventions such as anticancer, antioxidant, and anti-inflammatory activities with minimal adverse effects by suitable chemical substitution.

selenium selenoproteins lymphoma hematopoiesis selenocompounds

1. Introduction

Cancer is the leading cause of death worldwide. “In 2020, approximately 1,806,590 new cancer cases and 606,520 cancer deaths are projected to occur in the USA, which translates into about 1663 deaths per day” [1]. Despite recent advances in current ongoing precision cancer treatments including standard chemotherapy, radiation therapy, surgery, immunotherapy, hormone therapy, and targeted therapy, complete remission remains a challenge for most cancer patients due to the huge heterogeneity and mutational burden in cancer cells. In addition, the adverse effects associated with current anticancer therapeutics highlight the need for the development of novel therapeutic agents, natural compounds, and the inclusion of dietary supplements such as trace elements and nutraceuticals along with current treatment regimens to minimize the toxicity [2][3][4]. Among different trace elements, Se has gained tremendous attention these days due to its anticancer effects specifically in tumor cells, most probably mediated through regulation of cellular redox homeostasis, and dose-limiting cytotoxicity of other chemo agents [5].

Selenium (Se) is an essential micronutrient and its beneficial roles in promoting human health have been extensively reviewed in the past [5][6][7][8][9][10][11]. Though Se is an integral part of human metabolism, it is toxic at high concentrations if consumed like other trace elements. Generally, the intake of Se is through dietary food or external supplements and is utilized by the selenium metabolic system in the form of selenite and selenoaminoacids such as selenomethionine (SeMet) and selenocysteine (SeC). SeC is the 21st amino acid that

was first discovered by Chambers et al. while investigating the role of animal glutathione peroxidases (GPxs), and incorporated into selenoproteins (SePs) via the decoding of UGA by tRNA[Sec] [12]. As of now, 25 genes that encode for SePs are annotated in the human genome. The most known SePs include glutathione peroxidases (GPx1/GPx2/GPx3/GPx4/GPx6), iodothyronine deiodinases (DIO1/DIO2/DIO3), thioredoxin reductases (TrxR1/TrxR2/TrxR3), selenoprotein P (SelP), and selenophosphate synthase 2 (SPS2). Most of these SePs are redox-active enzymes that exhibit catalytic or antioxidant activity through SeC. Moreover, these SePs take part in several cellular processes such as deoxyribonucleoside triphosphate (dNTP) synthesis, redox homeostasis, protein folding, anti-inflammatory activity, thyroid hormone production, and Se transport and storage. The GPx and TRx constitute antioxidant systems and are involved in redox signaling, respectively, while deiodinases are involved in thyroid hormone metabolism. The glycoprotein selenoprotein P (SelP) is involved in Se transport in the plasma and constitutes an antioxidant defense against lipid peroxidation/free radicals [13][14]. The reactive oxygen species (ROS) and reactive nitrogen species (RNS) are byproducts of normal cellular metabolism and have a variety of effects on cellular functions, signaling, and homeostasis. The low levels of ROS/RNS have beneficial effects by promoting cell proliferation and longevity, whereas high ROS/RNS concentrations have detrimental effects by damaging DNA, proteins, and lipids and thus promote disease development and malignancy transformation. Therefore, the precise regulation of free intra- and extracellular ROS by different antioxidants and specific regulatory pathways plays an important role in maintaining cellular integrity. SePs, including GPxs and TRxs, play a critical role in achieving redox homeostasis, thus avoiding oxidative stress by neutralizing free ROS/RNS [15].

2. Biological Role of Se and SePs in Hematopoiesis and Lymphoma

2.1. Role of Se and SePs in Hematopoiesis

Hematopoiesis is a complex process of blood cell formation, which has a high demand for nutrients due to the rapid turnover time and shorter life span of these cells in the circulation. Hematopoiesis occurs during embryonic development and throughout adulthood to produce and replenish the blood system. In adults, the hematopoietic stem cells (HSCs) proliferate by self-renewal and differentiate into different blood lineages such as erythrocytes, leucocytes (basophils, eosinophils, lymphocytes, monocytes, and neutrophils), and platelets [16]. ROS are byproducts of normal cellular metabolism and have a variety of effects on cellular functions, signaling, and homeostasis. Therefore, the precise regulation of free intra- and extracellular ROS by different antioxidants and specific regulatory pathways plays an important role in maintaining cellular integrity. SePs, including GPxs and TRxs, play a critical role in achieving redox homeostasis, thus avoiding oxidative stress by neutralizing free ROS. As reviewed by Kaweme NM et al., the dysregulation of redox systems plays a critical role in both acute-, and chronic homological malignancies [17]. The process of Hematopoiesis requires tight redox regulation in order to avoid oxidative stress and thus hematological disorders. In fact, Marcus Conrad M et al. deciphered the essential role of mitochondrial TRx2 in hematopoiesis and cardiac development by using ubiquitous Cre-mediated inactivation of TrxR2 in mouse models. The mice lacking mitochondrial TrxR2 exhibited embryonic lethality with a drastic reduction in hematopoietic colonies along with cardiomyocyte proliferation [18].

In addition to redox regulation in HSCs during hematopoiesis, the erythropoiesis (production of new erythrocytes) process is constantly prone to oxidative stress due to the presence of iron, heme, and unpaired globin chains in erythrocytes, which are detrimental to erythroid development and can lead to anemia. The beneficial role of Se and SePs in stabilizing the erythropoiesis process through GPxs has been reviewed in [19]. Earlier, it was reported that the dietary supplementation of Se protects erythrocytes from oxidative damage in animal models and loss of SePs leads to hemolysis of erythrocytes. The extensive study by Liao C et al. explored the critical role of dietary Se and SePs in stress erythropoiesis using murine models. It was found that the loss of SePs functionality either by Se deficiency or mutation of the Sec tRNA (tRNA[Sec]) gene (*Trsp*) affected stress erythropoiesis at two stages. In line, the researchers correlated these findings with the loss of selenoprotein W (SelW), and SelW mutations in bone marrow cells and the murine erythroblast (G1E) cell line resulted in defective terminal differentiation [20]. The deficiency of Se or lack of SePs drastically affects the stress erythropoiesis intensifying the anemia in rodents and human patients. Therefore, the micronutrient Se and SePs play a critical role in the development and expansion of hematopoietic and erythroid cells, in addition to the erythroid niche during acute anemia recovery by neutralizing oxidative stress produced by excessive ROS generation.

2.2. Role of Se and SePs in Lymphoma

As cited above, Se is an important micronutrient that mediates a range of biological functions through SePs and, thus, affects the overall quality of human health. Accordingly, the deficiency of Se in serum is linked with aberrant immune functions, cancer, cardiac, and inflammatory diseases [21]. Recently, researchers reviewed the anticancer effects of Se and SeCs alone or in combination with standard therapy (chemo- or radiation) for different hematological malignancies including Leukemias [22]. The supplementation of Se and/or Se-containing food was shown to have chemopreventive effects in animals and humans with some contradictory reports [23]. In 2003, Last KW et al. analyzed Se levels in the sera frozen at presentation, from 100 lymphoma patients who received chemo-, radiation therapy, or both, using inductively coupled plasma mass spectrometry. Interestingly, their findings concluded that Se levels in the serum at presentation could act as a prognostic factor, predicting positively dose delivery, treatment response, and long-term survival in diffuse large B-cell lymphoma [24]. Based on the findings, the researchers have hypothesized that the Se supplementation might provide a novel treatment strategy for aggressive non-Hodgkin's lymphoma. In a similar line, Deffuant C et al. tested the predictive value of serum Se levels before and after therapeutic response in 200 melanoma (81 stage I, 63 stage II, and 56 stage III) and 51 epidermotropic cutaneous T-cell lymphoma (CTCL) (8 stage I, 24 stage II, 10 stage III, and 9 stage IV) patients using atomic absorption spectrophotometry. The study findings clearly demonstrated that serum Se levels have prognostic values in the follow-up of both melanoma and CTCL [25].

The study by Ozgen et al. reported that the Se level in hair was significantly lower in children with lymphoma or leukemia when compared to that of the healthy control group [26]. On a similar note, decreased serum Se levels were well correlated in adult patients with hematological malignancies such as acute myeloid leukemia (AML) [27] or advanced chronic lymphocytic leukemia (CLL) [28], while increased or normalized serum Se levels in AML patients were found following complete remission [27][29]. This evidence is further supported by testing the hypothesis in a large cohort of patients with hematological malignancies in a study by Stevens J et al. The

researchers included a total of 430 patients (163-AML; 156-Hodgkin Lymphoma; and 111-Follicular Lymphoma) to test serum Se levels. Interestingly, the treatment response was in accordance with serum levels of Se, and low levels of Se correlated with worse outcomes in hematological malignancies, but it was not independently predictive [30].

Se and SePs play important role in achieving cellular redox homeostasis. It was reported previously that cellular oxidative stress negatively impacts the chemotherapy of cancers. The researchers tested four different chemotherapy drugs (Ara-C, cisplatin, doxorubicin, and VP-16) to induce apoptosis in human Burkitt lymphoma cells and found out that H_2O_2-induced oxidative stress negatively impacts their therapeutic response [31]. So, the use of antioxidants could enhance chemotherapy-induced apoptosis and phagocytosis in the treatment of lymphomas and other cancers. In growing evidence, a recent study by Wu W et al. analyzed the expression of gene-encoding SePs in different types of cancer (between/within). The findings clearly demonstrated that the expression of SePs genes correlated well with tumor mutagenicity, drug sensitivity, and drug resistance. Further, SePs could be considered as potential therapeutic targets for the treatment of different cancers [32]. Accordingly, the overexpression of one of the SePs, glutathione peroxidase 4 (*GPX4*; an enzyme that suppresses peroxidation of membrane phospholipids) was shown to be a poor prognostic predictor of DLBC lymphomas. Very recently, it was ruled out that the downstream regulator of *GPX4*, namely, *SECISBP2* (Selenocysteine Insertion Sequence-Binding Protein 2), which regulates various SePs as a novel prognostic predictor, might be a novel therapeutic target for DLBC lymphomas treatment [33]. Altogether, these studies highlighted the role of biological levels of Se and SePs in prognosis, disease progression, and treatment response in hematological malignancies including lymphomas.

2.3. Effect of Se Supplementation in Patients Undergoing Hematopoietic Stem Cell Transplantation

Hematopoietic stem cell transplantation (HSCT) is one of many effective supportive cares for the treatment of several hematological disorders including lymphoma. Despite recent advances in the understanding of transplant immunology, HSCT has limitations due to severe complications such as graft-versus-host disease (GVHD), hepatic veno-occlusive disease, oral mucositis (OM), and infections [34]. These complications are triggered by pro-inflammatory cytokines, such as interleukins (IL-6/IL-1b) and tumor necrosis factor-alpha (TNF-α), released due to high-dose chemotherapy (HDC) prior to HSCT [35][36]. The ROS and oxidative stress (OS) produced by chemotherapy drugs are known to activate transcriptional factors including NF-kB, which, in turn, upregulate genes, which results in increased pro-inflammatory cytokines. Accordingly, the agents including Amifostine and TNF-α inhibitors that suppress oxidative stress (OS) or pro-inflammatory cytokine levels have been demonstrated to prevent or ameliorate complications related to HSCT [37][38]. Since Se has anti-inflammatory properties [39] and constitutes an important role in the human antioxidant system in the form of SePs (GPx/TRx), Daeian N et al. explored the effect of Se supplementation on pro-inflammatory cytokine levels in a randomized double-blind placebo-controlled clinical trial involving 74 patients undergoing HSCT. According to study findings, Se supplementation prevented severe OM in HSCT patients without exhibiting significant differences in the plasma

levels of inflammatory cytokines. So, the researchers concluded that earlier administration and/or using larger doses of Se might result in beneficial effects during HSCT [40].

3. Physico-Chemical and Anticancer Properties of Se

3.1. The Historical Perspectives of Se

In the year 1817, Jons Jacob Berzelius first isolated, identified, and analyzed the Se element [6]. After analyzing the properties of Se, interestingly, Marco Polo, in 1295, described the first record of Se toxicity and described a disease called “hoof rot” in cattle and horses in the Tien Shan and Nan Shan mountains of Turkestan, where the soil concentration of Se was high [41][42]. Some studies reported in the 20th century showed that high levels of Se in soil were strongly associated with the gradual development of skin lesions, neuropathy in horses, sheep, cattle, and some of the plants such as the genera *Astragalus, Xylorrhiza, Oonopsis,* and *Stanleya* [43][44][45]. Se toxicity is also associated with diseases called “blind staggers”, the symptoms of which mainly include weight loss, blindness, ataxia, anorexia, and respiratory distress [46]. In the year 1950, Se was replaced by vitamin E in the diet of some experimental animals, which did not show any adverse, abnormal effects [47]. Se is considered an essential trace element, and this was confirmed through a pathological clinical condition known as KESHAN disease, which is mainly implicated by the inadequate levels of Se presence in the diet. Some of the early reports in the 20th century reported that potassium selenate (around a concentration of 300 µg/day) and selenium dioxide (3 mg/day) are promising drugs for the treatment of hematological malignancies [48]. Accordingly, recent studies have also strongly recommended Se and SeCs for the prevention of different types of cancers [5][49][50].

3.2. Physico-Chemical Properties of Se

Se exists in three allotropic forms, namely, a (1) Deep red crystal; (2) red amorphous powder; and (3) black vitreous form. Mostly, Se is insoluble in water while inorganic alkali selenites and selenates are soluble in water [51]. Se shares similar chemical properties with sulfur, and to a lesser extent with tellurium, all belonging to group 16 of the periodic table. Se and SeCs have a strong tendency to make complexes with heavy metals. SeCs such as selenate are the most stable oxidized form in alkaline and also oxidizing solutions among the other SeCs, and alkyl SeCs are among the least toxic compounds (dimethyl selenide and trimethyl selenide), and these are mainly released as products of detoxification of selenium in the body [52]. Se has the capability to alter sulfur into different forms of organic SeCs, which include mainly dimethylselenide and trimethylselenonium; mostly Se occurs as a form of selenides and selenocysteine at physiological pH [53].

3.3. The Rationale behind the Use of Se and SeCs as Anticancer Agents

Normally, healthy cells can be differentiated from cancer cells by a number of molecular, physiological, and pathological functions. Most healthy cells can exhibit tightly regulated systems and low steady states of ROS/RNS production and reducing equivalents, while in cancer cells, mainly increased levels of ROS production and reduced equivalents such as NADPH and NADH through several uncontrolled glycolysis processes are observed. In

general, cancer cells also exhibit irregular functions that are associated with the up- or down-regulation of protein synthesis, deregulated ROS generation, and enhanced antioxidant capacity to counteract ROS-induced cell death, etc. According to several recent studies, the induction of high levels of oxidative stress and downregulation of target genes involved in the antioxidant capacity within the tumor cells have shown to be a promising therapeutic strategy for the treatment of different cancers [54][55]. However, several recent plausible observations have been put forward that the therapeutic role of SeCs as potential anticancer agents is typically by inducing DNA strand breaks, cell cycle arrest, and apoptosis [50].

Recent findings from pre-clinical studies and human clinical trials have strongly associated preventive and therapeutic roles of Se in cancer therapeutic development in addition to inhibition of tumor progression. It was shown recently that the supplementation of a Se-rich diet significantly lowered the incidence of cancer in mice [56]. The anticancer effects of Se and SeCs are very diverse, but findings from earlier studies hinted that Se exhibits anticancer activity by increasing ROS production, thiol group modifications, and chromatin binding and modifications [55][56][57][58][59][60]. So, the anticancer activity of Se was majorly attributed to organic Se, and associated mechanisms include antioxidant and pro-oxidant activities in different cancers including breast, lung, colon cancers, etc. In addition, the anticancer activity of Se was exhibited through several mechanisms, which mainly included protection against DNA damage by dimethylbenz anthracene-induced aberration, which was shown mainly in breast, liver, and colon cancers [61][62]. According to recent reports, the selenomethionine (Se-met) compound is the most abundant form, showing the greatest biological activity and also the highest chemotherapeutic form [63]. Although the majority of literature encourages the use of Se and SeCs as anticancer agents either alone or in combination with standard therapy, a few contradictory studies have reported that Se alone failed to exhibit anti-cancer activity in randomized clinical trials and observational studies [64]. In addition, supplementation with Se has shown an increased risk of cancer and detrimental effects, with a widespread outbreak of acute Se toxicity [65][66]. The use of Se and SeCs as anticancer agents is limited due to poor pharmacokinetics such as rapid elimination from the body, narrow therapeutic window, and lack of distribution selectively [67]. So, the development of new formulations to enhance pharmacokinetics and the careful interpretation of results considering the distinct biological properties of organic and inorganic SeCs is necessary to avoid Se-mediated toxicity.

Several organo-selenium species have evolved as superior anticancer agents compared to natural SeCs: for example, “Ebselen”, is a synthetic drug that exhibits anticancer activities against different cancer types including breast, colon, and liver cancers. Ethaselen is a modified version of the parent molecule Ebselen, which showed an improved solubility and showed promising results against small lung carcinoma, and is currently in a phase-1 clinical trial [58][59][60][61]. SeCs also prevent free ROS generation sites, prevent the excess hydrogen peroxide that damages DNA, and also act as a nutrient, and maintain several physiological processes such as homeostasis, cell proliferation mechanisms, angiogenesis inhibition, and induction of apoptosis caused by the carcinogens to normal cells [14]. Se exhibits chemopreventive actions through the activation of apoptosis, mainly including the activation of multiple apoptotic pathways such as the activation of p53, specific Bax upregulation, and Bcl2 downregulation [68]. Some of the microarrays and genomic studies have reported Se to show strong anticancer activities through the activation of apoptosis and specific DNA damage [69].

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