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Selenium Action in Neuro-Oncology

Eduard Yakubov · Michael Buchfelder · Ilker Y. Eyüpoglu · Nic E. Savaskan

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Abstract The trace element selenium and selenocysteine-carrying selenoproteins play a pivotal role in the brain. Beside the essential function during development and maintenance of brain action, selenium has also been associated with several neurological and neuro-oncological conditions. Reliable supply of selenium is important since selenium compounds can affect tumor microenvironment and neoangiogenesis in malignant gliomas (WHO grade III and IV [glioblastoma, GBM]) via induction of apoptosis and alteration of matrix metalloproteinases expression. Here, we summarize recent findings focusing on the anti-toxicity and cancer-preventive properties of selenium and their implication in current multimodal therapies including temozolomide (Temodal), cyclophosphamide (Endoxan), and cisplatin (DDP, Platiblastin, and Platinol). We shed light on unintended side effects in chemotherapy and the developments of novel combinatorial chemotherapeutics with selenium compounds. We found that selenium and selenium compounds have dual action profiles with direct anti-cancer and chemotherapy-intensifier effects as well as neuroprotective and cytoprotective agents. Current selenium trials and selenium supplementation with focus on neuro-oncology will be discussed with regard to low-adequate-to-high/toxic selenium status.

Keywords Brain tumor · Glioblastoma · Novel chemotherapeutic compounds · Clinical trial · Vascular endothelial growth factor · Alternative therapy

E. Yakubov · M. Buchfelder · I. Y. Eyüpoglu · N. E. Savaskan (✉)
Department of Neurosurgery, Universitätsklinikum Erlangen, FAU—Friedrich-Alexander Universität Erlangen-Nürnberg, Schwabachanlage 6, 91054 Erlangen, Germany
e-mail: nicolai.savaskan@uk-erlangen.de

Introduction

Selenium is an essential micronutrient in vertebrates and is crucial for brain development and metabolism [1–4]. Although initially known for its toxic effects, selenium appeared also to be important in maintaining a number of vital functions in the body and current scientific interests in selenium raised mainly because of its health-promoting effects [5, 6]. These trials and in vitro studies led to the assumption that selenium not only can reduce the risk of cancer, but may also participate in many important processes relevant to tumor biology such as immunity, fertility, cell growth, reactive oxygen species signaling, and tumor microenvironmental modulation [7–10]. In humans, several clinical studies have been conducted to unravel the role of selenium supply as a chemopreventive agent (Table 1). These trials revealed that selenium in the clinical setting is a double-edged sword. The 'Selenium and Vitamin E Cancer Prevention Trial' (SELECT) sought to determine whether selenium supplements in combination with vitamin E could protect against the development of prostate cancer, but it was prematurely stopped due to futility analysis, not toxicity (of which there was very little) [11]. In a previous large skin cancer prevention trial, selenium was associated with a reduced risk for prostate cancer [12–14]. According to the National Cancer Institute, selenium acts an antioxidant that might directly help control cell damage as well as part of the catalytic domain of selenoenzymes with various essential cell functions with cancer prevention activity [12]. Furthermore, ongoing trials are proving the impact of selenium. This and other trials uncovered the difficulties of translating experimental selenium data into clinical settings (Table 1).

Malignant gliomas or high-grade gliomas are common types of primary brain tumors (e.g., WHO grade III [anaplastic astrocytoma, oligodendroglioma, oligoastrocytoma, and ependymoma] and grade IV [glioblastoma multiforme, GBM] gliomas) and with a median survival time of

Table 1 Summary of conducted and ongoing clinical trials using selenium or Se-compounds

Study	Country	Year	Study type	Study population	Duration of treatment (y)	Daily dose	Primary disease outcome	Results	Criticism	Reference
Linxian Cancer Prevention Study	China	1986	Primary prevention; randomized, double-blind, placebo-controlled intervention	29,584 poorly nourished men and women, aged 40–69 years	5.25	15 mg β-carotene, 30 mg α-tocopherol, 50 mg selenium yeast	Cancer	9 % reduction in total mortality; 13 % decrease in cancer mortality; 21 % decrease in stomach cancer deaths; 10 % decrease in cerebrovascular mortality (nonsignificant).		[98]
SU.VI.MAX	France	1994	Primary prevention; randomized, double-blind, placebo-controlled intervention	12,741 men and women, aged 35–60 years	8	6 mg β-carotene, 30 mg α-tocopherol, 120 mg vitamin C, 100 μg selenium, 20 mg zinc	Cancer, ischemic heart disease	Reduction in total cancer incidence and all-cause mortality in men but not in woman; significant protective effect of antioxidants in men. Increased melanoma risk upon antioxidant supplementation in women.		[99, 100]
Nutritional Prevention of Cancer (NPC) Study	USA	1996	Secondary prevention; randomized, double-blind, placebo-controlled intervention	1,312 men and women with history of basal or squamous cell carcinoma, aged 18–80 y	4.5	200 μg selenium yeast	Skin cancer, prostate cancer	No effect on incidence of skin cancer; 63 % reduction in prostate cancer incidence; reduction in total cancer mortality and total cancer incidence; chemopreventive effect of Se on cancer incidence in males with low baseline Se.		[12–14]
SELECT	USA	2001	Primary prevention; randomized, double-blind, placebo-controlled intervention	35,533 men aged 50 years or older	5.5	200 μg selenomethionin, 400 mg vitamin E	Prostate cancer	Prematurely terminated to to unintended side effects: No effect of Se on prostate cancer; Vitamin E increased prostate cancer risk (17 %); Selenium increased the risk of high-grade prostate cancer among men with high selenium status;	Application form, initial Se serum levels already normal [135 μg/l]; at the terminatio n to high Se serum levels [above 220 μg/l]	[11, 101]
SELENIB	UK	2006	Randomized, placebo-controlled, double-blind.	500 patients with non muscle-invasive bladder cancer	5	200 μg selenium, 154 mg α- tocopherol	Bladder cancer	Ongoing trial, no results yet		
SELEBLAT	Belgium	2008	Tertiary prevention; randomized, placebo-controlled, multicentre, academic, double-blind superior trial	100 men and women aged 46–88 y with non-invasive transitional cell carcinoma of the bladder on TURB operation	3	200 μg selenium yeast	Bladder cancer	Ongoing trial, no results yet		[102]

approximately 1 year, belong to the most threatening tumor entities [15].

Especially, in this disease condition, there is urgent need for improving current medical practice for better outcome in terms of life expectancy and quality of life. Experimental and some clinical data suggested the efficacy of selenium application in malignant gliomas. Therefore, the aim of this paper is to investigate the current state-of-knowledge of selenium compounds in relation to malignant gliomas and the efficacy of selenium in current chemotherapy. For this, we performed a systematic literature search of PubMed (www.ncbi.nlm.nih.gov/pubmed) and Clinical Trials (www.clinicaltrials.org). English articles were primarily considered if not otherwise stated. Research articles and reviews were identified using the key words 'glioma,' 'brain tumor,' and 'selenium,' either alone or in combination. The relevant papers identified by this search were reviewed, and the references therein were further considered for other useful leads.

Selenium and its Biological Forms

The indispensable micronutrient selenium (Se) is available mainly in two forms, i.e. inorganic and organic. Inorganic Se forms include selenite (SeO_3^{2-}) and selenate (SeO_4^{2-}). The main organic forms are selenocysteine (SeC), selenomethionine (SeMet), and Se-methylselenocysteine (MSC). In addition to these compounds, experimental studies revealed the efficacy of the stable Se compound methylselenic acid which represents the simplest β–lyase version of Se-methylselenocysteine lacking the amino acid moiety [16, 17].

Selenium is metabolized dynamically and can be linked to in vivo combinatorial chemistry forming a wide array of products with different intracellular environment effects [18]. This may also explain why Se and Se compounds can have both beneficial as well as undesirable effects. A key metabolite of selenium in organisms is hydrogen selenide (H_2Se) which is formed from inorganic sodium selenite (SSe) via selenodiglutathione (GSSeSG) through reduction by thiols and NADPH-dependent reductases, and released from SeC by lyase action [19, 20]. H_2Se undergoes methylation by thiol S-methyltransferase as a major pathway for Se metabolism in microbes, plants, and animals and generate different methylated metabolic Se forms. At low Se doses, monomethylated forms of Se are excreted mainly into urine, while trimethylated forms are being predominant at high doses. When the level of trimethylselenonium ions reaches the metabolic plateau, dimethylselenide is exhaled by breath producing a characteristic garlic breath [21].

Hence, in organisms inorganic selenium is not simply stored, instead it is utilized in selenoprotein synthesis into specific selenoproteins that have incorporated the twenty-first genetically coded amino acid SeC under a precise process requiring the UGA codon, a specified tRNA and the SeC insertion sequence (SECIS) element [22, 23]. There are at least 25 selenoproteins coded in the human genome [24, 25]. Within the 25 selenoproteins, there are essential proteins such as glutathione peroxidases (GPx1, 4), thioredoxin reductases (TRx), selenoprotein P, selenoenzymes R, and deiodinases. In particular, GPx isoenzymes are implicated in cellular protection against damage caused by oxygen free radicals and redox dysbalances, with each isoenzyme having a specific location and specificity [26–29]. TRx play an essential role in antioxidant processes but are also implicated in the regulation of certain transcription factors and in gene expression [30]. GPx and TRx catalyze the reduction of hydrogen peroxide to eliminate harmful reactive oxygen species from the tissues and protect biological membranes and large molecular structures from oxidative damage [31].

Non-specific incorporation of Se into proteins occurs through substitution of SeMet for methionine. SeMet is the major constituent of selenized yeast (selenium yeast) used in chemopreventive studies [32] (Table 1).

Selenoproteins in the Brain

Several selenoproteins and selenoprotein activities (mainly glutathionperoxidase (GPx)) are present in human and rodent brains [2, 33, 34]. However, detailed cellular brain mapping of selenoprotein localization in terms of neurons, ependymal cells, and glial cells throughout the brain remains to be conducted. For instance, GPx isoenzymes, with the exception of GPx4, cannot be distinguished solely on grounds of substrate specificity and immunocytochemistry revealed PhGPx/GPx4 exclusively in neurons, while GPx/GPx1 is ubiquitously expressed in both neurons and astrocytes [27].

The major selenium transport form in plasma is selenoprotein P (SePP). SePP is generated in the liver releasing plasma SePP. Deletion of SePP showed severe consequences for the brain, inducing selenium-deficiency with neurological dysfunction under suboptimal nutritional selenium supply [35, 36]. SePP mRNA has been detected in human, rat, mouse, and bovine brain. Controversy surrounds the function of SePP within the brain. Clear evidences for SePP expression in the brain come from initial in situ hybridization and immunohistochemical studies demonstrating SePP mRNA in cerebellar Purkinje cells of mice and cattles [2, 37]. Moreover, SePP has been identified as the essential component in bovine serum that is necessary for maintaining neurons in serum-free media [38].

More recent studies considered SePP as a physiological transporter of Se from liver to brain. Hence, SePP can be found in grey and white matter and in cerebrospinal fluid suggesting SePP as a Se storage form in the brain [39]. However, SePP cannot rapidly load and unload Se as a simple cargo since selenium is covalently incorporated as the amino

acid selenocysteine (SeC) which requires degradation to release Se. SeC depends on the lysosome or proteasome to hydrolyze peptide bonds followed by liberation of Se from SeC, presumably by SeC lyase (SeCly). Recently, a study in mice suggests that SePP is more critical than SeCly for maintenance of brain Se and that recycling Se from SeC via SeCly is physiologically important during dietary Se deficiency [40]. As Se supply becomes limited, alternative routes of its hepatic metabolism decrease, allowing continued SePP synthesis for export into the plasma [41]. SePP in plasma provides Se to extra-hepatic tissues via ApoER2-mediated endocytosis and plays an important role for the protection against Se deficiency [42].

Consequences of Selenium Deficiency in Human Health

Selenium (Se) plays a vital part in many essential functions for humans. However, the functions of Se as an antioxidant trace element are considered to be carried out under physiological conditions by selenoproteins that possess antioxidant activities and the ability to promote neuronal cell survival. There selenium plays a pivotal role in the formation and function of selenocysteine-bearing selenoproteins, such as glutathione peroxidase (GPx) for antioxidant protection of cells [43]. Several studies indicated that sufficient Se intake could improve the human immune system and prevent tumor growth by enhancing immune cell activity and suppressing development of blood vessels to the tumor [12, 44, 45]. What is relevant is that the activity of these selenoproteins, and of others with as yet unidentified functions, depends on adequate selenium supply either via nutritional entry or by therapeutic interventions.

Selenium deficiency can lead to human diseases such as Keshan disease and Kashin-Beck disease. Although the etiology of Keshan disease (KD) is not fully understood, it has been recognized by most researchers that KD is strongly associated with selenium deficiency [46]. This statement is based on evidence that the Se levels in soil and food in the external environment of the endemic area are significantly lower than those in the non-endemic area. Blood and hair Se levels, the activity of GPx and the antioxidative capacity of patients with KD is also significantly lower than those in healthy individuals. In particular, the incidence of KD significantly decreased after Se supplementation.

Selenium in Primary Brain Tumors

The first clinical evidence for selenium in neuro-oncology came from one report on decreased serum concentrations of selenium in patients suffering from brain malignancies [47]. Gliomas are the most common primary brain tumor in the central nervous system derived from glial cells or glial progenitors, with WHO grade IV gliomas (glioblastoma, GBM) as the most malignant form with a median survival below 14 months from the time point of diagnosis [48]. Malignant gliomas demonstrate rapid progression and are highly resistant to standard treatment, resulting in a particularly poor prognosis in patients. These tumors are distinct from other cancer types by exhibiting profound vascularization, necrosis, brain swelling (edema), and microvascular hyperplasia. Pseudopalisades and microvascular hyperplasia are indicative of aggressive growth and are instrumental in malignant progression [49]. Pseudopalisading cells also produce proangiogenetic factors such as vascular endothelial growth factor (VEGF), which promote endothelial proliferation and angiogenesis. Furthermore, endothelial cells respond to the angiogenic signal by increasing the production of matrix metalloproteinases (MMPs), such as MMP-2. The increased MMP levels are associated with poor prognosis in malignant glioma patients. MMP-2 can cleave laminin 5 γ2 and release proteolytic fragments which are capable of leading to tumor cell invasion and prevention of tumor cell apoptosis via epidermal growth factor receptor (EGFR) [50]. EGFR contributes to cell proliferation, revival, motility, and invasion and is often overexpressed in gliomas. There is evidence that selenite can decrease the EGFR expression in vitro [51]. Using glioma cells A-172 to evaluate the anti-tumor activity of a mixture of nutrient compounds, which contained several antioxidants including Se, Roomi et al. demonstrated that the nutrient mixture significantly reduced the invasion of glioma cells and the secretion of MMP-2 in a dose-dependent manner [52].

In biopsy specimens of an anaplastic astrocytoma, Rooprai et al. showed that selenite induced apoptosis and extensive changes in the expression of MMPs [51]. Most MMPs (except MMP-25) were reduced and their natural inhibitor tissue inhibitor of metalloproteinase (TIMP) increased [51]. In line with this are the findings of Yoon et al. reporting that selenium prevents migration of endothelial cells through the extracellular matrix (ECM) and blocks MMP expression and tumor invasion [53]. Future studies are required to decipher the anti-tumor effect of selenium on malignant gliomas. In principle, two mechanisms need to be considered: Selenium action could be directly mediated through apoptosis induction or by specific alteration of the MMP expression profiles which affects glioma cell survival secondarily.

Selenium and Chemotherapy

Cancer chemotherapy has been shown to play an important role in the treatment of most solid tumors, although this therapeutic approach has also been associated with substantial short- and long-term side effects (Fig. 1). These side effects impact significantly on the quality-of-life in cancer patients. A growing body of evidence suggests that a combinatorial treatment of chemotherapy and chemo-preventive agents with anti-carcinogenic activity may enhance the efficacy of

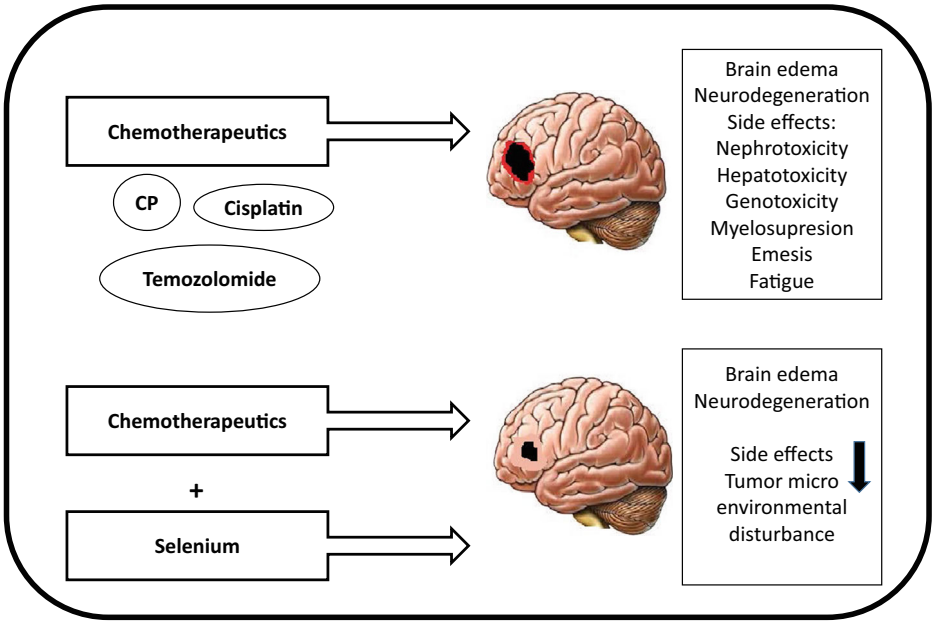

Fig. 1 Selenium, brain tumor microenvironment, and chemotherapeutic therapies. Current chemotherapeutics in neuro-oncology are depicted in the scheme. Unintended side effects with serious consequences are given (boxes at the right) which are common in neuro-oncology. Also, the impact of therapeutics on the tumor microenvironment is indicated, such as brain edema, neuronal cell death, and angiogenesis. Brain tumor is depicted in *black*, peritumoral zone and tumor microenvironment is shown in *red*. Abbreviations: *CP* cyclophosphamide; *TMZ* temozolomide, *Se* selenium

chemotherapeutics and reduce the systemic toxicity induced by chemotherapy [54–56]. Selenium (Se) is essential to human health, but its role as a chemopreventive agent was for a long-time controversial. However, recent studies are in support of chemo-preventive and cancer-preventive properties of selenium according to clinical, epidemiologic, and experimental studies [57–59]. Although most research efforts on Se have focused on prevention of tumor initiation and promotion [60], there are a number of studies indicating the ability of Se compounds to enhance the efficacy of standard chemotherapeutic drugs [61–63], such as cyclophosphamide, cisplatin, and temozolamide (Fig. 1).

Cyclophosphamide (CP), an agent frequently employed for its chemotherapeutic effects in cancer treatment, is a cytostatic and immunosuppressive drug. The efficacy of CP in treating brain tumors has been limited by the fact that although CP crosses the blood–brain barrier, its active metabolites are only poorly transported across this barrier [64]. CP is a pro-drug that undergoes bioactivation mainly by CYP-3A4 and CYP-2B6 to produce reactive metabolites such as acrolein and phosphoramide mustard [65]. The active form of CP is an alkylating agent and causes disruption of cell growth, mitotic activity, differentiation, and function by cross-linking of DNA strands. In addition to carcinogenic potential, CP has a wide spectrum of toxicities [66]. However, numerous studies have shown that CP exposure enhances intracellular reactive oxygen species (ROS) production, suggesting that biochemical and physiological disturbances may result from oxidative stress [67–70]. These reactive oxygen species damage DNA, proteins, and cellular lipids leading to cell death [71]. Antioxidants are known to be responsible for enzyme reduction, molecular repair (superoxide dismutase, catalase, and glutathione peroxidase), and protection against ROS [72]. The combination of CP together with a potent antioxidant may be the appropriate approach to reduce the toxicity effects of CP [73]. However, among those antioxidants, selenium is involved in several key metabolic activities via selenoproteins, enzymes that are essential for protection against oxidative damage, and the regulation of immune function. Depending on the dose, selenium attenuates the toxic effect of CP, and it also attenuates CP-induced oxidation stress and DNA damage [74]. More recently, Bhattacharjee et al. reported that nano-Se protects against hepatotoxicity and genotoxicity induced by CP. These data suggest that the mechanisms of hepatoprotection by nano-Se against CP-induced toxicity and hepatic damage involve suppression of oxidative stress by preventing glutathione depletion [75]. We suggest that at the appropriate concentration, selenium could be a potentially effective modulator of CP toxicity (Fig. 1). However, additional experiments are required to explore the underlying mechanism of selenium protection against CP toxicity and the therapeutic window.

The platinum compounds cisplatin and carboplatin are cell cycle nonspecific, bi-functional alkylating agents with demonstrated efficacy in adult and pediatric malignancies including brain tumors [76–78]. Cisplatin is a potent toxin for cells. It enters into cells, gets hydrolyzed, and then binds to DNA leading to cellular toxicity (Fig. 1). However, this goes along with increased risks for renal toxicity which is dose-dependent, and thus limits its usage [79, 80]. The use of carboplatin as an alternative to cisplatin in several adult and pediatric solid tumors has increased in the last 20 years in view of emerging

evidence for its efficacy and lower nephrotoxic potential [81]. Moreover, preclinical and early clinical studies in adults suggested that carboplatin causes much less renal damage than cisplatin [82, 83].

Many strategies have attempted to prevent or reduce the nephrotoxicity side effects of chemotherapeutics [84, 85]. Animal studies also suggest that cisplatin nephrotoxicity may be reduced by a variety of antioxidants including capsaicin, glutamine, melatonin, and *N*-acetylcysteine [86]. Furthermore, a survey of the literature reveals in particular the protective effects of Se against cisplatin-induced renal damage [20, 87].

Temozolomide (TMZ) is currently used as an upfront treatment for newly diagnosed and recurrent glioblastoma multiforme (GBM), and is also utilized for treating patients with metastatic melanoma due to its ability to penetrate through the blood–brain barrier and does not require hepatic metabolism for activation [88, 89]. TMZ is known to enhance the responsiveness of GBM to radiation in preclinical testing, and the action of concurrent TMZ at the time of radiotherapy is likely to be responsible for most of the treatment effects [90]. Furthermore, TMZ is an imidazotetrazine derivate and a novel oral alkylating agent with enhanced cytotoxicity for fast growing cells. DNA replication disruption is the principal mechanism responsible for the cytotoxic activity of TMZ, resulting in the fragmentation of DNA and defects in DNA replication, and in consequence to cell growth suppression and apoptotic cell death [91, 92]. A relevant number of malignant brain tumors are TMZ-resistant or acquire resistance via O^6-methylguanine-DNA methyltransferase (MGMT) promoter methylation, as evidenced by therapeutic failure in some malignant glioma patients who still die within 2 years under therapy. Cheng et al. tested incorporating Se into TMZ (TMZ-Se) demonstrating superior anti-tumor activity. Researchers reported the effectiveness of this compound even against TMZ-resistant tumor cells. The comparison between TMZ and TMZ-Se showed in vitro a greater inhibitory effect on proliferating glioma cells with TMZ-Se and growth suppression of tumors in xenograft animal models. These reports indicate that TMZ-Se triggers cell-death more rapidly, possesses stronger apoptosis-inducing activity and induced stronger autophagic response than solely TMZ (Fig. 2). Notably, there are potentially two roles of Se in current chemotherapy: First, Se and Se compounds can reduce toxicity in multimodal tumor therapy. Second, Se and Se compounds can act as a sensitizer and enhancer/multiplier for conventional chemotherapeutic treatment regiments (Fig. 2). Both aspects need to be evaluated further in clinical trials. Obviously, simply reducing chemotherapeutic toxicity with simultaneous reducing efficacy is not a desirable outcome.

Taken together, the mechanism of action of Se compounds has an effective chemo-protective impact that should be taken into account especially in the case of TMZ-resistant tumors [93].

However, selenium at high concentrations (serum Se levels above 200 μg/l) has also negative impact on cellular functions. This fact should be kept in mind when supplementing Se with inorganic or novel Se-coupled pharmacological agents in clinical settings. High Se intake can be toxic and have adversely effect on the integrity of genomic DNA in various tissues and organs [94]. Although the mechanisms responsible for the adverse effects of high doses of Se are not completely understood, the effects can be severe with DNA damage, oxidative stress, and cell death induction [95–97]. On the other side, balanced levels of Se are required for cell survival and growth (Fig. 2). Due to the prospective

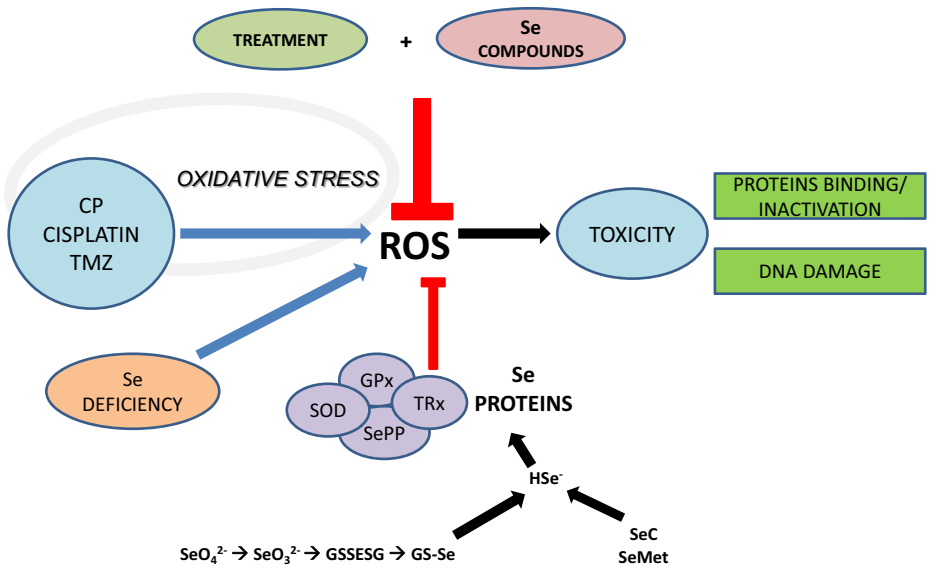

Fig. 2 Dual actions of selenium in neuro-oncology. Summary of Se actions on glioma cells. First, Se can act directly as a reducing agent against ROS formation induced by chemotherapeutics thereby restricting collateral damages. Second, Se is incorporated into selenoproteins such as GPx, SePP, and TRx. These selenoenzymes are known to balance ROS levels and execute cell protective functions. Abbreviations: *GPx* glutathione peroxidase; *Se* selenium; *SePP* selenoprotein P; *SOD* superoxiddismutase; *TRx* thioredoxin reductase

use of Se in clinical practice, further studies are necessary to elucidate the mechanisms of toxicity and the therapeutic window for selenium compounds.

Conclusion

Taking into account the outcome of this current literature and clinical trial research paper, we can conclude that selenium is largely implicated in antioxidant defense mechanisms, redox signaling, and immune function. Investigations show so far that insufficient selenium levels are associated with disadvantageous health effects and in the context of disease, with tumor progression. Notwithstanding that epidemiological data and clinical trials do not give an unambiguous picture for selenium supplementation many studies suggest that selenium, and its compounds are promising chemo-preventive and anti-cancer agents. The unambiguous results of clinical trials surrounding selenium do not only foster our knowledge of chemo-preventive efficacy, but also increase the efforts to understand its molecular mechanisms and interactions with conventional therapeutics. Investigations on the efficacy of selenium in malignant gliomas are further required. So far, data support the notion that the investigation of selenium and selenium compounds shows considerable properties, which places selenium at the center for future research on preventive or therapeutic agents in neurological conditions.

References

1. Brauer AU, Savaskan NE (2004) Molecular actions of selenium in the brain: Neuroprotective mechanisms of an essential trace element. Rev Neurosci 15(1):19–32
2. Schweizer U, Brauer AU, Kohrle J, Nitsch R, Savaskan NE (2004) Selenium and brain function: a poorly recognized liaison. Brain Res Brain Res Rev 45(3):164–178
3. Pillai R, Uyehara-Lock JH, Bellinger FP (2014) Selenium and selenoprotein function in brain disorders. IUBMB Life 66 (4):229–239
4. Byrns CN, Pitts MW, Gilman CA, Hashimoto AC, Berry MJ (2014) Mice lacking selenoprotein P and selenocysteine lyase exhibit severe neurological dysfunction, neurodegeneration, and audiogenic seizures. J Biol Chem 289(14):9662–9674
5. Bleys J, Navas-Acien A, Guallar E (2008) Serum selenium levels and all-cause, cancer, and cardiovascular mortality among US adults. Arch Intern Med 168(4):404–410
6. Ray AL, Semba RD, Walston J et al (2006) Low serum selenium and total carotenoids predict mortality among older women living in the community: the women's health and aging studies. J Nutr 136 (1):172–176
7. Carlson BA, Yoo MH, Shrimali RK et al (2010) Role of selenium-containing proteins in T-cell and macrophage function. Proc Nutr Soc 69(3):300–310
8. Hall JA, Vorachek WR, Stewart WC et al (2013) Selenium supplementation restores innate and humoral immune responses in footrot-affected sheep. PLoS One 8(12):e82572
9. Naziroglu M, Senol N, Ghazizadeh V, Yuruker V (2014) Neuroprotection induced by N-acetylcysteine and selenium against traumatic brain injury-induced apoptosis and calcium entry in hippocampus of rat. Cell Mol Neurobiol 34(6):895–903
10. Streicher KL, Sylte MJ, Johnson SE, Sordillo LM (2004) Thioredoxin reductase regulates angiogenesis by increasing endothelial cell-derived vascular endothelial growth factor. Nutr Cancer 50(2):221–231
11. Kristal AR, Darke AK, Morris JS et al (2014) Baseline selenium status and effects of selenium and vitamin E supplementation on prostate cancer risk. J Natl Cancer Inst 106(3):djt456
12. Clark LC, Combs GF Jr, Turnbull BW et al (1996) Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. Nutritional Prevention of Cancer Study Group. JAMA 276(24):1957–1963
13. Clark LC, Dalkin B, Krongrad A et al (1998) Decreased incidence of prostate cancer with selenium supplementation: Results of a double-blind cancer prevention trial. Br J Urol 81(5):730–734
14. Duffield-Lillico AJ, Reid ME, Turnbull BW et al (2002) Baseline characteristics and the effect of selenium supplementation on cancer incidence in a randomized clinical trial: a summary report of the Nutritional Prevention of Cancer Trial. Cancer Epidemiol Biomarkers Prev 11(7):630–639
15. Wen PY, Kesari S (2008) Malignant gliomas in adults. N Engl J Med 359(5):492–507
16. Ip C, Thompson HJ, Zhu Z, Ganther HE (2000) In vitro and in vivo studies of methylseleninic acid: evidence that a monomethylated selenium metabolite is critical for cancer chemoprevention. Cancer Res 60(11):2882–2886
17. Qi Y, Fu X, Xiong Z et al (2012) Methylseleninic acid enhances paclitaxel efficacy for the treatment of triple-negative breast cancer. PLoS One 7(2):e31539
18. Ganther HE (1999) Selenium metabolism, selenoproteins and mechanisms of cancer prevention: complexities with thioredoxin reductase. Carcinogenesis 20(9):1657–1666
19. Ganther HE (1971) Reduction of the selenotrisulfide derivative of glutathione to a persulfide analog by glutathione reductase. Biochemistry 10(22):4089–4098
20. Husain K, Morris C, Whitworth C, Trammell GL, Rybak LP, Somani SM (1998) Protection by ebselen against cisplatin-induced nephrotoxicity: Antioxidant system. Mol Cell Biochem 178(1–2):127–133
21. Itoh M, Suzuki KT (1997) Effects of dose on the methylation of selenium to monomethylselenol and trimethylselenonium ion in rats. Arch Toxicol 71(7):461–466
22. Papp LV, Lu J, Holmgren A, Khanna KK (2007) From selenium to selenoproteins: Synthesis, identity, and their role in human health. Antioxid Redox Signal 9(7):775–806
23. Patterson BH, Zech LA (1992) Development of a model for selenite metabolism in humans. J Nutr 122(3 Suppl):709–714
24. Kryukov GV, Castellano S, Novoselov SV et al (2003) Characterization of mammalian selenoproteomes. Science 300 (5624):1439–1443
25. Loscalzo J (2014) Keshan disease, selenium deficiency, and the selenoproteome. N Engl J Med 370(18):1756–1760
26. Castellano S, Lobanov AV, Chapple C et al (2005) Diversity and functional plasticity of eukaryotic selenoproteins: Identification and characterization of the SelJ family. Proc Natl Acad Sci U S A 102 (45):16188–16193
27. Savaskan NE, Borchert A, Brauer AU, Kuhn H (2007) Role for glutathione peroxidase-4 in brain development and neuronal apoptosis: Specific induction of enzyme expression in reactive astrocytes following brain injury. Free Radic Biol Med 43(2):191–201

28. Savaskan NE, Ufer C, Kuhn H, Borchert A (2007) Molecular biology of glutathione peroxidase 4: from genomic structure to developmental expression and neural function. Biol Chem 388 (10):1007–1017
29. Ufer C, Wang CC, Fahling M et al (2008) Translational regulation of glutathione peroxidase 4 expression through guanine-rich sequence-binding factor 1 is essential for embryonic brain development. Genes Dev 22(13):1838–1850
30. Beckett GJ, Arthur JR (2005) Selenium and endocrine systems. J Endocrinol 184(3):455–465
31. Battin EE, Brumaghim JL (2009) Antioxidant activity of sulfur and selenium: a review of reactive oxygen species scavenging, glutathione peroxidase, and metal-binding antioxidant mechanisms. Cell Biochem Biophys 55(1):1–23
32. Uden PC, Bird SM, Kotrebai M et al (1998) Analytical selenoamino acid studies by chromatography with interfaced atomic mass spectrometry and atomic emission spectral detection. Fresenius J Anal Chem 362(5):447–456
33. Trepanier G, Furling D, Puymirat J, Mirault ME (1996) Immunocytochemical localization of seleno-glutathione peroxidase in the adult mouse brain. Neuroscience 75(1):231–243
34. Zhang Y, Zhou Y, Schweizer U et al (2008) Comparative analysis of selenocysteine machinery and selenoproteome gene expression in mouse brain identifies neurons as key functional sites of selenium in mammals. J Biol Chem 283(4):2427–2438
35. Hill KE, Zhou J, McMahan WJ et al (2003) Deletion of selenoprotein P alters distribution of selenium in the mouse. J Biol Chem 278(16):13640–13646
36. Schomburg L, Schweizer U, Holtmann B, Flohe L, Sendtner M, Kohrle J (2003) Gene disruption discloses role of selenoprotein P in selenium delivery to target tissues. Biochem J 370(Pt 2):397–402
37. Saijoh K, Saito N, Lee MJ, Fujii M, Kobayashi T, Sumino K (1995) Molecular cloning of cDNA encoding a bovine selenoprotein P-like protein containing 12 selenocysteines and a (His-Pro) rich domain insertion, and its regional expression. Brain Res Mol Brain Res 30 (2):301–311
38. Yan J, Barrett JN (1998) Purification from bovine serum of a survival-promoting factor for cultured central neurons and its identification as selenoprotein-P. J Neurosci 18(21):8682–8691
39. Scharpf M, Schweizer U, Arzberger T, Roggendorf W, Schomburg L, Kohrle J (2007) Neuronal and ependymal expression of selenoprotein P in the human brain. J Neural Transm 114 (7):877–884
40. Raman AV, Pitts MW, Seyedali A et al (2012) Absence of selenoprotein P but not selenocysteine lyase results in severe neurological dysfunction. Genes Brain Behav 11(5):601–613
41. Hill KE, Wu S, Motley AK et al (2012) Production of selenoprotein P (Sepp1) by hepatocytes is central to selenium homeostasis. J Biol Chem 287(48):40414–40424
42. Kurokawa S, Hill KE, McDonald WH, Burk RF (2012) Long isoform mouse selenoprotein P (Sepp1) supplies rat myoblast L8 cells with selenium via endocytosis mediated by heparin binding properties and apolipoprotein E receptor-2 (ApoER2). J Biol Chem 287(34):28717–28726
43. Ellis DR, Salt DE (2003) Plants, selenium and human health. Curr Opin Plant Biol 6(3):273–279
44. Reid ME, Duffield-Lillico AJ, Slate E et al (2008) The nutritional prevention of cancer: 400 mcg per day selenium treatment. Nutr Cancer 60(2):155–163
45. Wallace K, Kelsey KT, Schned A, Morris JS, Andrew AS, Karagas MR (2009) Selenium and risk of bladder cancer: a population-based case–control study. Cancer Prev Res 2(1):70–73
46. Tan JA, An WY, Li RB (1987) The geo-medical characteristics of Keshan disease. Keshan disease prevention and treatment in China, pp 254–264
47. Philipov P, Tzatchev K (1988) Selenium concentrations in serum of patients with cerebral and extracerebral tumors. Zentralbl Neurochir 49(4):344–347
48. DeAngelis LM (2001) Brain tumors. N Engl J Med 344(2):114–123
49. Brat DJ, Castellano-Sanchez AA, Hunter SB et al (2004) Pseudopalisades in glioblastoma are hypoxic, express extracellular matrix proteases, and are formed by an actively migrating cell population. Cancer Res 64(3):920–927
50. Giannelli G, Falk-Marzillier J, Schiraldi O, Stetler-Stevenson WG, Quaranta V (1997) Induction of cell migration by matrix metalloprotease-2 cleavage of laminin-5. Science 277(5323): 225–228
51. Rooprai HK, Kyriazis I, Nuttall RK et al (2007) Inhibition of invasion and induction of apoptosis by selenium in human malignant brain tumour cells in vitro. Int J Oncol 30(5):1263–1271
52. Roomi MW, Ivanov V, Kalinovsky T, Niedzwiecki A, Rath M (2007) Inhibition of glioma cell line A-172 MMP activity and cell invasion in vitro by a nutrient mixture. Med Oncol 24(2):231–238
53. Yoon SO, Kim MM, Chung AS (2001) Inhibitory effect of selenite on invasion of HT1080 tumor cells. J Biol Chem 276(23): 20085–20092
54. Sarkar FH, Li Y (2006) Using chemopreventive agents to enhance the efficacy of cancer therapy. Cancer Res 66(7):3347–3350
55. Uğuz AC, Naziroğlu M, Espino J et al (2009) Selenium modulates oxidative stress-induced cell apoptosis in human myeloid HL-60 cells through regulation of calcium release and caspase-3 and −9 activities. J Membr Biol 232:15–23
56. Kahya MC, Nazıroğlu M, Ciğ B (2014) Selenium reduces mobile phone (900 MHz)-induced oxidative stress, mitochondrial function, and apoptosis in breast cancer cells. Biol Trace Elem Res 160(2): 285–293
57. Sugie S, Tanaka T, El-Bayoumy K (2000) Chemoprevention of carcinogenesis by organoselenium compounds. J Health Sci 46(6): 422–425
58. Whanger PD (2004) Selenium and its relationship to cancer: an update. Br J Nutr 91(1):11–28
59. Zhou N, Xiao H, Li TK, Nur EKA, Liu LF (2003) DNA damage-mediated apoptosis induced by selenium compounds. J Biol Chem 278(32):29532–29537
60. Jung HJ, Seo YR (2010) Current issues of selenium in cancer chemoprevention. Biofactors 36(2):153–158
61. Chintala S, Toth K, Cao S et al (2010) Se-methylselenocysteine sensitizes hypoxic tumor cells to irinotecan by targeting hypoxia-inducible factor 1 alpha. Cancer Chemother Pharmacol 66(5): 899–911
62. Hu H, Li GX, Wang L, Watts J, Combs GF Jr, Lu J (2008) Methylseleninic acid enhances taxane drug efficacy against human prostate cancer and down-regulates antiapoptotic proteins Bcl-XL and survivin. Clin Cancer Res 14(4):1150–1158
63. Tan Q, Li J, Yin HW et al (2010) Augmented antitumor effects of combination therapy of cisplatin with ethaselen as a novel thioredoxin reductase inhibitor on human A549 cell in vivo. Invest New Drugs 28(3):205–215
64. Wei MX, Tamiya T, Chase M et al (1994) Experimental tumor therapy in mice using the cyclophosphamide-activating cytochrome P450 2B1 gene. Hum Gene Ther 5(8):969–978
65. Roy P, Yu LJ, Crespi CL, Waxman DJ (1999) Development of a substrate-activity based approach to identify the major human liver P-450 catalysts of cyclophosphamide and ifosfamide activation based on cDNA-expressed activities and liver microsomal P-450 profiles. Drug Metab Dispos 27(6):655–666
66. Fraiser LH, Kanekal S, Kehrer JP (1991) Cyclophosphamide toxicity. Characterising and avoiding the problem. Drugs 42(5): 781–795
67. Chabra A, Shokrzadeh M, Naghshvar F, Salehi F, Ahmadi A (2014) Melatonin ameliorates oxidative stress and reproductive toxicity

induced by cyclophosphamide in male mice. Hum Exp Toxicol 33 (2):185–195
68. Das UB, Mallick M, Debnath JM, Ghosh D (2002) Protective effect of ascorbic acid on cyclophosphamide-induced testicular gametogenic and androgenic disorders in male rats. Asian J Androl 4(3): 201–207
69. Ghosh D, Das UB, Ghosh S, Mallick M, Debnath J (2002) Testicular gametogenic and steroidogenic activities in cyclophosphamide treated rat: a correlative study with testicular oxidative stress. Drug Chem Toxicol 25(3):281–292
70. Manda K, Bhatia AL (2003) Prophylactic action of melatonin against cyclophosphamide-induced oxidative stress in mice. Cell Biol Toxicol 19(6):367–372
71. Korkmaz A, Topal T, Oter S (2007) Pathophysiological aspects of cyclophosphamide and ifosfamide induced hemorrhagic cystitis; implication of reactive oxygen and nitrogen species as well as PARP activation. Cell Biol Toxicol 23(5):303–312
72. Behrman HR, Preston SL (1989) Luteolytic actions of peroxide in rat ovarian cells. Endocrinology 124(6):2895–2900
73. Selvakumar E, Prahalathan C, Sudharsan PT, Varalakshmi P (2006) Chemoprotective effect of lipoic acid against cyclophosphamide-induced changes in the rat sperm. Toxicology 217(1):71–78
74. Tripathi DN, Jena GB (2008) Ebselen attenuates cyclophosphamide-induced oxidative stress and DNA damage in mice. Free Radic Res 42(11–12):966–977
75. Bhattacharjee A, Basu A, Ghosh P, Biswas J, Bhattacharya S (2014) Protective effect of Selenium nanoparticle against cyclophosphamide induced hepatotoxicity and genotoxicity in Swiss albino mice. J Biomater Appl 29(2):303–317
76. Kornblith PL, Walker M (1988) Chemotherapy for malignant gliomas. J Neurosurg 68(1):1–17
77. Kyritsis AP (1993) Chemotherapy for malignant gliomas. Oncology 7(9):93–100
78. Pech IV, Peterson K, Cairncross JG (1998) Chemotherapy for brain tumors. Oncology 12(4):537–543, 547
79. Ghorbani A, Omidvar B, Parsi A (2013) Protective effect of selenium on cisplatin induced nephrotoxicity: a double-blind controlled randomized clinical trial. J Nephropathol 2(2):129–134
80. Nematbakhsh M, Ashrafi F, Pezeshki Z et al (2012) A histopathological study of nephrotoxicity, hepatoxicity or testicular toxicity: which one is the first observation as side effect of Cisplatin-induced toxicity in animal model? J Nephropathol 1(3):190–193
81. Doz F, Pinkerton R (1994) What is the place of carboplatin in paediatric oncology? Eur J Cancer 30A(2):194–201
82. Calvert AH, Harland SJ, Newell DR et al (1982) Early clinical studies with cis-diammine-1,1-cyclobutane dicarboxylate platinum II. Cancer Chemother Pharmacol 9(3):140–147
83. Foster BJ, Clagett-Carr K, Leyland-Jones B, Hoth D (1985) Results of NCI-sponsored phase I trials with carboplatin. Cancer Treat Rev 12(Suppl A):43–49
84. Cornelison TL, Reed E (1993) Nephrotoxicity and hydration management for cisplatin, carboplatin, and ormaplatin. Gynecol Oncol 50(2):147–158
85. Pinzani V, Bressolle F, Haug IJ, Galtier M, Blayac JP, Balmes P (1994) Cisplatin-induced renal toxicity and toxicity-modulating strategies: a review. Cancer Chemother Pharmacol 35(1):1–9
86. Sahni V, Choudhury D, Ahmed Z (2009) Chemotherapy-associated renal dysfunction. Nat Rev Nephrol 5(8):450–462
87. Naziroglu M, Karaoğlu A, Aksoy AO (2004) Selenium and high dose vitamin E administration protects cisplatin-induced oxidative damage to renal, liver and lens tissues in rats. Toxicology 195:221–230
88. Chamberlain MC (2010) Temozolomide: Therapeutic limitations in the treatment of adult high-grade gliomas. Expert Rev Neurother 10 (10):1537–1544
89. Omar AI, Mason WP (2010) Temozolomide: the evidence for its therapeutic efficacy in malignant astrocytomas. Core Evid 4:93–111
90. Chakravarti A, Erkkinen MG, Nestler U et al (2006) Temozolomide-mediated radiation enhancement in glioblastoma: a report on underlying mechanisms. Clin Cancer Res 12(15): 4738–4746
91. Carmo A, Carvalheiro H, Crespo I, Nunes I, Lopes MC (2011) Effect of temozolomide on the U-118 glioma cell line. Oncol Lett 2 (6):1165–1170
92. Gao S, Yang XJ, Zhang WG, Ji YW, Pan Q (2009) Mechanism of thalidomide to enhance cytotoxicity of temozolomide in U251-MG glioma cells in vitro. Chin Med J 122(11):1260–1266
93. Cheng Y, Sk UH, Zhang Y et al (2012) Rational incorporation of selenium into temozolomide elicits superior antitumor activity associated with both apoptotic and autophagic cell death. PLoS One 7 (4):e35104
94. Letavayova L, Vlckova V, Brozmanova J (2006) Selenium: from cancer prevention to DNA damage. Toxicology 227(1–2):1–14
95. Biswas S, Talukder G, Sharma A (2000) Chromosome damage induced by selenium salts in human peripheral lymphocytes. Toxicol In Vitro 14(5):405–408
96. Letavayova L, Vlasakova D, Spallholz JE, Brozmanova J, Chovanec M (2008) Toxicity and mutagenicity of selenium compounds in Saccharomyces cerevisiae. Mutat Res 638(1–2):1–10
97. Wycherly BJ, Moak MA, Christensen MJ (2004) High dietary intake of sodium selenite induces oxidative DNA damage in rat liver. Nutr Cancer 48(1):78–83
98. Blot WJ, Li JY, Taylor PR et al (1993) Nutrition intervention trials in Linxian, China: supplementation with specific vitamin/mineral combinations, cancer incidence, and disease-specific mortality in the general population. J Natl Cancer Inst 85(18):1483–1492
99. Hercberg S, Galan P, Preziosi P et al (2004) The SU.VI.MAX Study: a randomized, placebo-controlled trial of the health effects of antioxidant vitamins and minerals. Arch Intern Med 164(21): 2335–2342
100. Hercberg S, Ezzedine K, Guinot C et al (2007) Antioxidant supplementation increases the risk of skin cancers in women but not in men. J Nutr 137(9):2098–2105
101. Lippman SM, Klein EA, Goodman PJ et al (2009) Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA 301(1):39–51
102. Goossens ME, Buntinx F, Joniau S et al (2012) Designing the selenium and bladder cancer trial (SELEBLAT), a phase lll randomized chemoprevention study with selenium on recurrence of bladder cancer in Belgium. BMC Urol 12:8