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Review

Strategies for the development of selenium-based anticancer drugs

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ABSTRACT

Many experimental models demonstrated that inorganic and organic selenium (Se) compounds may have an anticancer activity. However, large clinical studies failed to demonstrate that Se supplementations may prevent the outcome of cancers. Moreover, there are few randomized trials in cancer patients and there is not yet any Se compound recognized as anticancer drug. There is still a need to develop new Se compounds with new strategies. For that, it may be necessary to consider that Se compounds may have a dual role, either as anti-oxidant or as pro-oxidant. Experimental studies demonstrated that it is as pro-oxidant that Se compounds have anticancer effects, even though cancer cells have a pro-oxidant status. The oxidative status differs according to the type of cancer, the stage of the disease and to other parameters. We propose to adapt the doses of the Se compounds to markers of the oxidative stress, but also to markers of angiogenesis, which is strongly related with the oxidative status. A dual role of Se on angiogenesis has also been noted, either as pro-angiogenesis or as anti-angiogenesis. The objective for the development of new Se compounds, having a great selectivity on cancer cells, could be to try to normalize these oxidative and angiogenic markers in cancer patients, with an individual adaptation of doses.

1. Introduction

Selenium (Se) compounds are generally considered as anti-oxidants. These effects are mediated by selenoproteins, which contain selenocysteine (SeCys), that may be replaced by cysteine (Cys) in the conditions of low Se status [1]. Cys is a containing sulfur (S) aminoacid, with a thiol (SH) group and it is the precursor of Glutathion (GSH). The Se analogue of Cys is SeCys, with a replacement of the S atom by a Se one [2]. Se-based proteins have a greater reactivity than the corresponding sulfur derivatives [3]. The selenoprotein P (SELENOP for humans, SelenoP for mouse), synthesized in the liver, has a great number of SeCys residues which allow the retention of Se and its transport from the blood to the tissues. The Glutathion peroxidases (GPX), the Glutathion Reductase (GR), the Thioredoxin Reductases (TXNRD or TrxR), are selenoproteins with oxidoreductases functions catalyzing the reduction of disulfide (S-S) bonds in proteins and peptides, providing reductive properties [4]. Antioxidant selenoproteins maintain the intracellular redox status in healthy cells. They protect them and it has been shown that very low doses (1–10 nM) of sodium selenite (Na_2SeO_3) or of selenomethionine (SeMet) (10–50 nM) could prevent the cell death induced by Reactive Oxygen Species (ROS) in cultured human skin cells [5]. The anti-oxidant system protects the SH groups from oxidation or reduces disulfides (S-S) when SH groups have been oxidized by free radicals [6]. The oxido-reductions reactions have to be strictly regulated in order to maintain a normal redox potential. During the oxidation induced by free radicals, electrons are removed, with an increase in the oxidation state and the cells become oxidized. An antioxidant is a reducing agent, giving electrons to a free radical. The oxidation always involves a corresponding reduction reaction and on the other side the reduction reaction always needs an oxidation reaction: oxidations and reductions always go together and are called redox reactions. The oxido-reductions reactions include redox couples [7], among them cysteine/cystine, reduced glutathione (GSH)/oxidized glutathione disulphide (GSSG), reduced nicotinamide adenine dinucleotide (NAD)/oxidized nicotinamide adenine dinucleotide (NADH), reduced nicotinamide adenine dinucleotide phosphate (NADP)/oxidized nicotinamide adenine dinucleotide phosphate (NADPH), reduced flavin adenine dinucleotide (FAD)/oxidized $FADH_2$). The X_c^- exchanger cystine-glutamate participates in the intracellular-extracellular cysteine/cystine redox cycle, favouring the cystine uptake, and its reduction to Cys in the cell but also the secretion of Cys into the extracellular space [8]. Cys is derived either from extracellular cystine via the X_c^- exchanger or from methionine (Met) via a transsulfuration pathway [6]. The SH groups of Cys and Met may be oxidized by free radicals [9], but there are many other thiol-containing proteins. Park et al. identified 194 reactive thiol-containing proteins in prostate cancer cells, among them 94 could be modified by a Se compound [10]. The oxidation reactions occuring in proteins may be reversible or non-reversible. The redox potential or reduction potential (E) reflects the concentrations of the reduced and oxidized forms of a given reaction

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pair. It is expressed in volts (V) as it represents an energy, for the fluxes of electrons. For example, the redox potential of cysteine/cystine has been measured as 140–160 mV in the cytosol, and of 80 mV extracellularly, while the redox potential of GSH/GSSG was 230 mV intracellularly and 140 mV extracellularly [6]. The overall redox potential of cells can also be determined, and all redox potentials can be measured accurately. However, the concentration conditions are specific of the cells. Finally, changes in the cellular or extracellular redox potentials for a specific cell will induce biological effects, activating or deactivating protein activity and function [6]. They affect signaling pathways and transcriptional processes and involve redox-sensitive phosphatases, protein kinases, and transcription factors [11].

The two main metabolites of Se compounds are methylselenol (CH_3SeH) and hydrogen selenide (H_2Se). H_2Se is one of the major intermediary metabolites of inorganic Se compounds while organic Se will mainly form methylated metabolites [12]. CH_3SeH has a strong nucleophilicity [10] and its anionic form is selenolate. With low concentrations of Se, the selenoproteins have antioxidant effects. In contrast, with high Se doses, the formation of CH_3SeH, selenolate and H_2Se metabolites will increase and they may react with oxygen and SH to produce superoxide and hydrogen peroxide [13,14], which will be toxic for the cells [3]. Redox couples can either be oxidized or reduced by Se, depending on the influence of neighboring groups and redox potential [10].

The oxidative stress is the result of the equilibrium between the production of free radicals and the anti-oxidant defence system. Free radicals are Reactive Oxygen Species (ROS), especially superoxide and hydroperoxides, Reactive Nitrogen Species (RNS), especially Nitric Oxide (NO) and Reactive Sulfur Species (RSS). The production in excess of free radicals favours the development of cancer [15,16], but they are also required to eliminate damaged cells in a safe organism and to allow an optimal function of the immune system. Low doses of ROS allow a normal homeostasis, high doses induce a tumor inhibition and between them, the levels of ROS may favour the development of cancer [17]. Concerning RNS, both promoting and inhibiting actions have also been described, at least for NO [18], which is derived from the oxidative deamination of L-arginine to L-citrulline by NO synthases (NOS). NOS are specifically involved in NO/peroxynitrite signaling pathways [19]. TrxR can change from an anti- to a pro-oxidant [20], and selenoproteins can act as oncosuppressors, but can also, on the contrary, favour the formation of malignant tumors [21]. Selenoprotein expression may either suppress or promote tumorigenesis [22], depending on cell type and genotype [23]. Se appears to be a redox potential modulator with a dual role on the oxidative stress. Finaly, Se appears to be a redox potential modulator with a dual role on the oxidative stress.

2. Oxidative stress and cancer

Oxidation-reduction reactions in cancer cells are in favour of cellular oxidation with a higher rate than cellular reduction [24]. The antioxidant system cannot counteract the excessive production of free radicals, resulting in a pro-oxidant status of the cancer cells, with an increase of the redox potential. The redox ratio of cancer cells can be measured by assaying the endogenous fluorescence intensity of NADH and of FAD by optical methods and the ratio of FAD/(FAD + NADH) determined in four isogenic triple-negative breast cancer cell lines showed that the increase in the metastatic potential was correlated with an increase of the redox potential [25]. The redox potential differs according to the type of cancer. There is a good correlation between the histology and the redox potential of cancer cells, with even the possibility to determine the molecular subtype of breast cancers according to the redox status of the cancer cells [26]. In human prostate carcinoma cells in culture, it was shown that the oxidative status was different between the more invasive PC3 cells and the LNCaP cells, according to the levels of hydroxy-2′-deoxyguanosine, the GSH/GSSG ratio and to the levels of both ROS and RNS intracellularly and in the medium [27]. The prominent role of extracellular redox in cell invasion ability has also been demonstrated in an other in vitro study with DU145, PC-3, RWPE1-derived human prostate cancer (WPE1-NB26) cell lines compared with RWPE1 cells (immortalized, but nonmalignant prostate epithelial cells) [28]. The distinction between luminal type cancer, cells expressing Human Epidermal Growth Factor (HER2) and triple negative cancer cells has been related to the oxidative status, but also to markers of inflammation [29], with high levels of lipidic peroxidation and of NO [30]. The HER2 overexpression influences the oxidant/antioxidant parameters in breast cancer patients [31]. The expression of NOS is enhanced in many tumors and particularly the iNOS isoform (calcium-independent and inducible) [18]. The enhanced oxidative/nitrosative stress observed in breast cancer patients could also be responsible of the induction of a prooxidant environment in the adjacent mammary gland [32]. Even at an early stage of surgical breast cancer, there is an enhanced oxidative stress characterized by high lipid peroxidation, total antioxidant capacity of plasma (TRAP) consumption, high carbonyl content, elevated Vascular Endothelial Growth Factor (VEGF) and Tumor Necrosis Factor (TNF-α) levels [33]. After tumor removal, the levels of lipid peroxidation, malondialdehyde (MDA) content, VEGF, and TNF- α decreased. The pro-oxidant status is more pronounced when the stage of the cancer disease is more advanced [34]. In head and neck cancer patients [35], the ratio of GSSG/GSH was increased in patients with positive nodes (N1/N2/N3) versus those with negative node (N0). In metastatic melanoma patients, there was an increase of MDA, TRAP, thiol, advanced oxidation protein products (AOPP) in plasma and an increase in lipid peroxidation levels in eythrocytes, with a good correlation between the Tumor Growth Factor (TGF-β1) and the oxidative stress [36]. There is an increase of the oxidative status under the effects of chemotherapeutic agents like doxorubucin or paclitaxel [37], or of endocrine therapy (antiestrogens, and aromatase inhibitors) [11]. A decrease of the content of anti-oxydant enzymes in the cancer cells could decrease the efficacy of a chemotherapy by carboplatin/paclitaxel [38]. A relationship has been observed between the degree of resistance to a cytotoxic drug and the oxidative system in a cisplatin-resistant prostate cancer model [39]. Levels of AOPPs, TRAP and reduced total thiol increased under the influence of trastuzumab in patients treated for HER2-amplified breast tumors [40]. An other study also showed that trastuzumab induced apoptosis and oxidative stress [41]. The extracellular space has a more oxidized redox state than inside the cells under physiological conditions, but in the case of cancer the extracellular redox state may also be altered, with an important relationship between the extracellular redox state and the cancer cell aggressiveness [42]. There is no standardized method for evaluating oxidative status and many tests have been proposed, but it appears important to select those that may assayed in the plasma of cancer patients and to analyze their variations under the influence of the cancer treatment, which can be a Se-based anticancer drug.

3. Dual role of Se on the oxidative stress

Se compounds may have either antioxidant and pro-oxidant properties, depending on experimental conditions [43], and mainly on their concentrations [44]. The effects of Se on cancer cells are highly concentration-dependent, and low to moderate levels may stimulate growth, whereas higher levels are cytotoxic [45]. According to the dose, the effects of a Se compound may be greatly different [46]. Se at low essential level (nM) is required for synthesis of redox active selenoenzymes such as GPX and TXNRD, but at higher toxic levels ($> 5–10\ \mu M$) sodium selenite (Na_2SeO_3) can react with essential SH groups on enzymes to form RS-Se-SR adducts with a resultant inhibition of the enzyme activities [47]. It is known that Se stimulates the growth of cells in culture at low doses [48] and fetal calf serum which is commonly used in cell cutures was estimated to contain about 17 ng Se/ml [49]. Therefore, it is non usual to evaluate the stimulating effects of Se compounds on the cell growth in vitro experiments. On the other