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Review

Selenium compounds as therapeutic agents in cancer ☆

Aristi P. Fernandes [a,*], Valentina Gandin [b]

[a] Division of Biochemistry, Department of Medical Biochemistry and Biophysics (MBB), Karolinska Institutet, SE-171 77 Stockholm, Sweden
[b] Department of Pharmaceutical and Pharmacological Sciences, University of Padova, Via Marzolo 5, 35131 Padova, Italy

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ABSTRACT

Background: With cancer cells encompassing consistently higher production of reactive oxygen species (ROS) and with an induced antioxidant defense to counteract the increased basal ROS production, tumors have a limited reserve capacity resulting in an increased vulnerability of some cancer cells to ROS. Based on this, oxidative stress has been recognized as a tumor-specific target for the rational design of new anticancer agents. Among redox modulating compounds, selenium compounds have gained substantial attention due to their promising chemotherapeutic potential.

Scope of review: This review aims in summarizing and providing the recent developments of our understanding of the molecular mechanisms that underlie the potential anticancer effects of selenium compounds.

Major conclusions: It is well established that selenium at higher doses readily can turn into a prooxidant and thereby exert its potential anticancer properties. However, the biological activity of selenium compounds and the mechanism behind these effects are highly dependent on its speciation and the specific metabolic pathways of cells and tissues. Conversely, the chemical properties and the main molecular mechanisms of the most relevant inorganic and organic selenium compounds as well as selenium-based nanoparticles must be taken into account and are discussed herein.

General significance: Elucidating and deepening our mechanistic knowledge of selenium compounds will help in designing and optimizing compounds with more specific antitumor properties for possible future application of selenium compounds in the treatment of cancer. This article is part of a Special Issue entitled Redox regulation of differentiation and de-differentiation.

1. Introduction

Selenium (Se) is an essential and unique trace element that plays a crucial role in health and disease. Se exerts many cellular physiological functions mediated by its incorporation into selenoproteins, mainly in the form of selenocysteine (Sec), the 21st amino acid. The human genome harbors 25 selenoprotein genes (for more comprehensive reading on selenoproteins please see ref [1] and references therein). Some of these proteins are essential enzymes that do not only integrate Se in the form of Sec, but also requires Sec in their active site for an intact enzymatic activity (functions of Sec in selenoproteins are discussed in detail in the review by Arnér E.S. [2]). The antioxidant function of Se is conferred by some of these selenoproteins that directly protects against oxidative stress. Additionally, the regeneration and activation of low molecular weight antioxidants (Q10, Vitamins C and E etc.) mediated by selenoproteins, also make Se an indirect antioxidant, when provided at low nutritional levels [3]. However, at elevated doses, Se typically turns into a pro-oxidant with well-established growth inhibiting properties and with high cytotoxic activities (Fig. 1). Both efficacy and toxicity of Se compounds are thus strictly dependent on the concentration and chemical species as well as the redox potential [4]. Inorganic and organic selenium compounds metabolize differently in vivo, activating distinct molecular mechanisms responsible for the toxicity/activity profile, where the redox active forms have been shown to be far more effective [7]. However, the literature on the properties of Se and selenium compounds in cancer is confusing, to say the least, since it does not properly take into consideration that the distinct effects of Se strictly depend on compound, concentration and model used [5]. The main research on Se and cancer has been focused on the chemopreventive effects of selenium. This primary theory was grounded on the direct and indirect antioxidant functions of Se in non-transformed cells, which lead to a greater cellular defense against oxidative damages. At the same time, this hypothesis lays its basis on the ability of Se to "target" preneoplastic cells early in the carcinogenic process, as a cohort of evidence indicates that Se will turn into a pro-oxidant in these cells at lower concentrations than benign cells, making the preneoplastic cells more sensitive to Se supplementation. On the contrary, when exploring

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* Corresponding author at: Division of Biochemistry, Department of Medical Biochemistry and Biophysics, Karolinska Institutet, SE-171 77 Stockholm, Sweden. Tel.: +46 8 52486990.
E-mail address: aristi.fernandes@ki.se (A.P. Fernandes).

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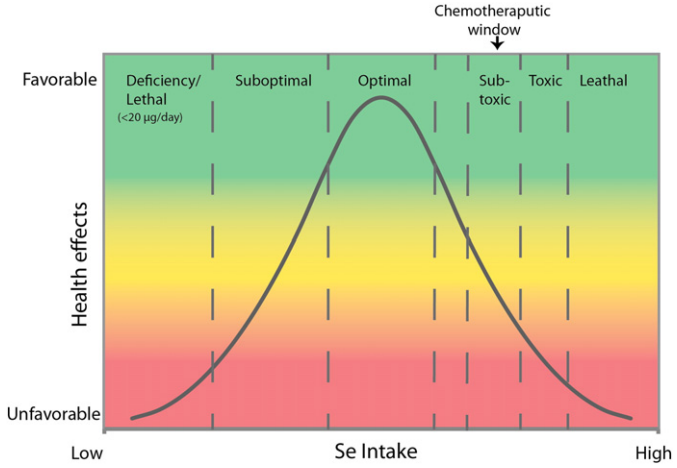

Fig. 1. A general biological response curve, illustrating the dose dependent effects of selenium compounds.

the chemotherapeutic effects of Se, the rational differs and is based on the assumption that progressed malignant cells have been found to be more sensitive to Se cytotoxicity than normal cells. Despite the fact that higher doses are required to encounter the pro-oxidative effects of Se, with the generation of oxidative stress being a requirement for a favorable outcome, the cytotoxic effects seem to appear at lower doses in malignant cells compared to benign cells. Consequently, selenium compounds have been highlighted in recent studies to have great potential as anticancer agents, particularly for the treatment of aggressive late stage neoplasias [6,7]. As tumor cells generally are more susceptible to the cytotoxic effects exhibited by selenium compounds, [7–9] at pharmacologically achievable doses, there seems to be a narrow therapeutic window for the use of selenium compounds as anticancer agents. This review aims at describing the proposed mechanisms and targets of selenium compounds and their effect in the treatment of established tumors. It will not, however, cover the largely debated chemopreventive properties of Se. This overview hopes to be a useful tool for the research community actively involved in the field of Se-based drug development and intends to shed light into their activity as chemotherapeutic agents.

2. The rational behind the use of selenium in cancer therapeutics

In general, healthy cells are characterized by a low steady-state level of ROS and in some way constant levels of reducing equivalents, while cancer cells are endowed with increased levels of ROS and reducing equivalents (e.g., NADPH, NADH) due to accelerated glycolysis (the Warburg effect) and pentose phosphate cycle. In addition, cancer cells develop an increased and maximized antioxidant capacity, as a compensatory mechanism to evade ROS-induced cell death that makes them extra vulnerable to an additional ROS induction. It is widely recognized that the balance between ROS and reducing equivalents in cells and tissues determines their redox state, and that it is detrimental to uphold the redox balance within the cell. The overall cellular redox state is tightly regulated by systems that modulate the cellular redox status by counteracting ROS, and/or by reversing the formation of disulfides. These systems are either dependent on the glutathione systems or on the thioredoxin (Trx) system [10]. Due to increasing evidence suggesting the vulnerability of cancer cells to oxidative stress, the idea of targeting the antioxidant capacity of tumor cells has risen as promising therapeutic strategy and has evolved as the rational design of new anticancer agents [11]. Among cancer cell redox modulators, selenium compounds gained substantial attention. Selenium compounds with antiproliferative properties, their tumor selectivity and mechanism of action are discussed below.

3. Selenium compounds (The structures of the selenium compounds discussed in this review are presented in Table 1.)

3.1. Inorganic

The most pertinent example of an inorganic selenium compounds evaluated as a therapeutic agent for the treatment of cancer can be found in the Se(IV) species selenite (SeO_3^{2-}). In several studies, it exhibited a significant cytotoxicity, in the low-micromolar range, against malignant cells, such as lung [12,13], prostate [14], cervical [15], ovarian [16] and colon [17,18] cancer cells, in primary human acute myeloid [19] and lymphoblastic [20] leukemia cells, as well as in hepatoma [21], melanoma [22] and mesothelioma cells [7]. Interestingly, different studies reported that drug-resistant cells are significantly more sensitive to selenite compared to their drug-sensitive counterparts [16,23]. In combination therapy, selenite potentiates the effects of camptothecin against cervical cancer cells [24], of 5-FU, oxaliplatin, and irinotecan in colon cancer cell lines [25], and of docetaxel towards prostate cancer cells [26]. In addition, this compound significantly enhances the effect of radiation on well-established hormone-independent prostate tumors [27]. In many of these studies selenite has been found selective towards drug resistant cells [12] and neoplastic cells rather than benign cells [7,8]. The mechanism accounting for this will be comprehensively discussed below.

In vivo experiments have confirmed the therapeutic potency of selenite on both solid [28] and lymphoproliferative models [29,30]. However, the efficacy of selenite is seriously hampered by its systemic and organ toxicities as well as by its genotoxic potential. Among other inorganic selenium forms, Se(IV) dioxide (SeO_2) has been found to exert a discrete in vitro cancer cell killing activity whereas compounds with higher Se oxidation state, such as Se(VI) selenate (SeO_4^{2-}), are hardly effective against mammalian cancer cells. Takahashi et al. showed that both selenite and selenium dioxide induced cell death in human oral squamous carcinoma cells, whereas selenate had no effect on cell survival [31].

3.2. Organic

3.2.1. Selenodiglutathione

The primary cellular metabolite of selenite, the thioselenide selenodiglutathione (SDG), was first tested in the 90s for its potential as an anticancer agent. Notably, many different studies carried out in a wide range of cancer cells concluded that it is a more powerful inhibitor of in vitro cancer cell growth than selenite [32–35]. Interestingly, cancer cells were found to be significantly more sensitive than normal cells to the antiproliferative activity of SDG, thus confirming the preferential activity of SDG against neoplastic cells. In spite of these very encouraging results, SDG was unexpectedly not further explored for its potential application as an anticancer agent, putatively due to the assumption that selenite and SDG exert their antiproliferative activity through similar molecular mechanisms, thus retaining similar adverse side effects, even though this has recently been shown not to be the case [36].

3.2.2. Selenoaminoacid derivatives

Despite the fact that the cancer preventive mechanisms of action of the aminoacidic derivative selenomethionine (SeMet) have been fairly studied, little has been done to evaluate its effect as antiproliferative agent. In recent studies, SeMet was shown to inhibit tumor growth of colorectal [37,38], lung [39,40], breast and prostate cancer cells as well as melanoma cells [41,42]. However, the Se-containing amino acid exerted its antitumor activity at much higher concentration (medium to high micromolar range) compared to Se redox active forms. Recent papers report on the potential of using SeMet in combination with ionizing radiation opening new promising prospective for its employment for the treatment of lung cancer [43].

Similar to SeMet, Se-methylselenocysteine (MSC) a monomethylated seleno-aminoacid, was highlighted as effective, at medium to high micromolar concentrations, in inhibiting cell proliferation of