Biochimica et Biophysica Acta 1850 (2015) 1642–1660

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbagen

Review

Selenium compounds as therapeutic agents in cancer ☆

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ARTICLE INFO

Article history:
Received 3 September 2014
Received in revised form 6 October 2014
Accepted 8 October 2014
Available online 16 October 2014

Keywords:
Selenium
Cell death
Chemotherapeutics

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

☆ This article is part of a Special Issue entitled Redox regulation of differentiation and de-differentiation.

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http://dx.doi.org/10.1016/j.bbagen.2014.10.008
0304-4165/

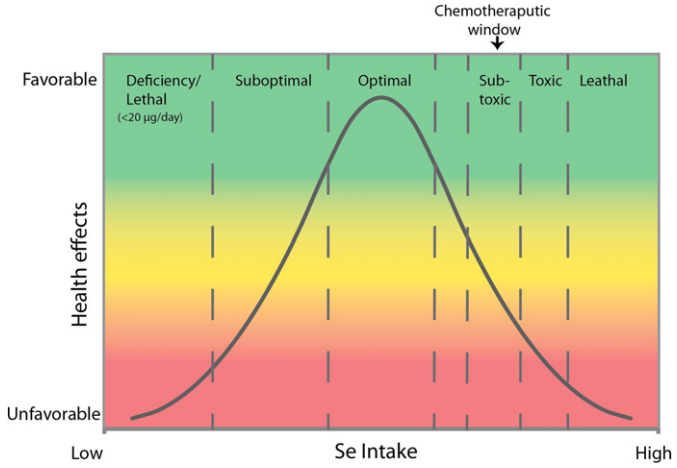


Fig. 1. A general biological response curve, illustrating the dose dependent effects of selenium compounds.

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

Table 1
Structure of selenium compounds and studies of their cytotoxic effects.

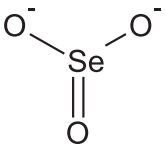
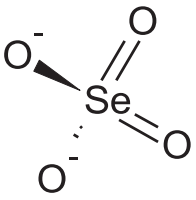
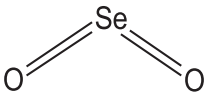
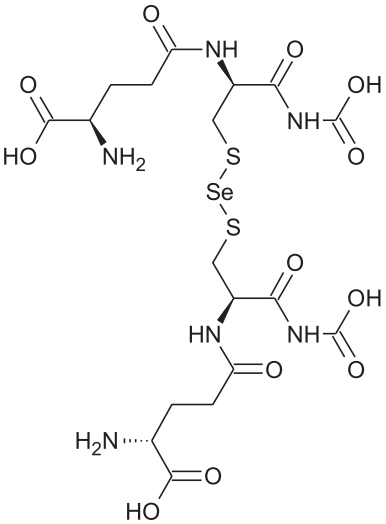
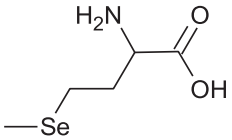
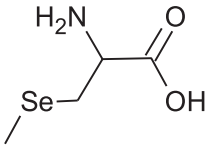
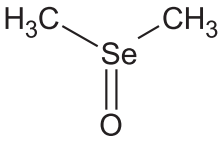
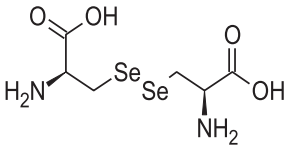
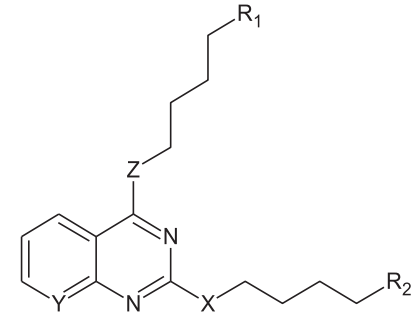
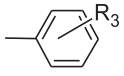
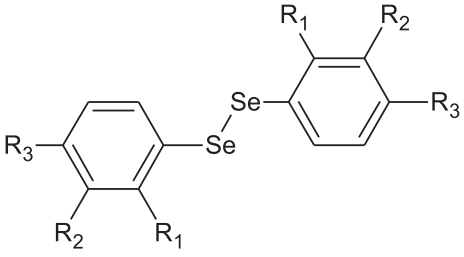
Selenium compounds [CAS number]	Structure	Biological models	Ref.
Selenite [Sodium selenite 10102-18-8]		*In vitro*	
		Human lung cancer cells	[12,13]
		Human prostate cancer cells	[14]
		Human cervical cancer cells	[15]
		Human ovarian cancer cells	[16]
		Human colon cancer cells	[17,18]
		Human primary acute myeloid and lymphoblastic leukemia cells	[19,20]
		Hepatoma cells	[21]
		Melanoma cells	[22]
		Mesothelioma cells	[7]
		In vitro combination therapy	
		Human cervical cancer cells (camptothecin)	[24]
		Human colon cancer cell (5-FU), oxaliplatin, and irinotecan	[25]
		Human prostate cancer cells (docetaxel)	[26]
		Human hormone-independent prostate tumors (radiation)	[27]
		In vivo	
		Human colorectal carcinoma	[28]
		Human promyelocytic leukemia	[29,30]
Selenate [Sodium selenate 13410-01-0]		*In vitro*	
		Human oral squamous cancer cells	[31]
Selenium dioxide [7446-08-4]		*In vitro*	
		Human oral squamous carcinoma cells	[31]
Selenodiglutathione (SDG) [33944-90-0]		*In vitro*	
		Human promyelocytic leukemia cells	[32]
		Mouse erythroleukemia cells and human ovarian cancer cells	[33]
		Mouse mammary epithelial cells	[34]
		Human oral carcinoma cells	[35]
		Human cervical cancer cells	[36]
Selenomethionine (SeMet) [3211-76-5]		*In vitro*	
		Human colorectal cancer cells	[37,39]
		Human lung cancer cells	[40]
		Human prostate cancer cells	[41,42]
		Human breast cancer cells	[42]
		Human melanoma cells	[42]
		In vitro combination therapy	
		Lung cancer cells (ionizing radiations)	[43]
Se-methylselenocysteine (MSC) [26046-90-2]		*In vitro*	
		Human oral squamous cells	[40]
		Human colon cancer cells	[44]
		Human breast cancer cells	[45]
		In vivo combination therapy	
		Human colorectal carcinoma and head and neck squamous cell carcinoma (cisplatin, oxaliplatin and irinotecan)	[48]
		Human head and neck squamous cell carcinoma (irinotecan)	[49]
		Human breast carcinoma (tamoxifen)	[50]

Table 1 *(continued)*

Selenium compounds [CAS number]	Structure	Biological models	Ref.
Methylseleninic acid (MSA) [28274-57-9]		*In vitro* Human lung cancer cells Human prostate cancer cells Human breast cancer cells Mouse mammary epithelial tumor cells *In vivo* Human and mouse prostate carcinomas *In vivo combination therapy* Triple-negative breast cancer (paclitaxel)	 [52] [53–56] [5] [57] [53,58] [59]
Selenocystine [29621-88-3]		*In vitro* Human melanoma cells Human cervical cancer cells Human lung cancer cells Human breast cancer cells *In vitro combination therapy* Human melanoma cells (5-FU) *In vivo* Human melanoma	 [61] [36] [38] [62] [63] [61]
Quinazoline and pyrido[2,3-d] pyrimidine selenium compounds	 Y = N, C X = S, Se Z = NH, O, Se R_1 = H, OH, CH_3,  R_3 = H, OCH_3, SCH_3, $SeCH_3$ R_2 = H, CH_3	*In vitro* Human leukemia cells Human colon, lung and breast cancer cells	 [64] [64]
Diselenides	 R_1 = H, OCH_3, NH_2 R_2 = H, CF_3 R_3 = H, OCH_3	*In vitro* Human leukemia cells Human neuroblastoma cells Human colon carcinoma cells	 [65] [66] [67]

(continued on next page)

Table 1 *(continued)*

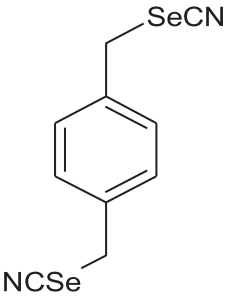
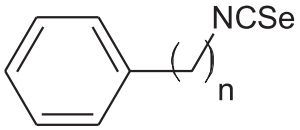
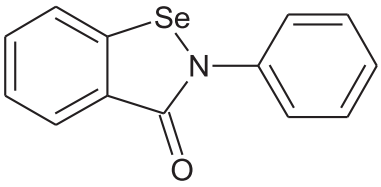
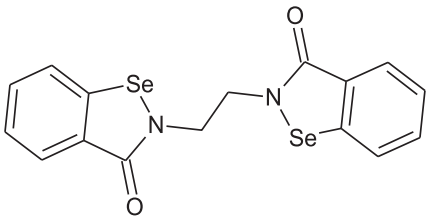
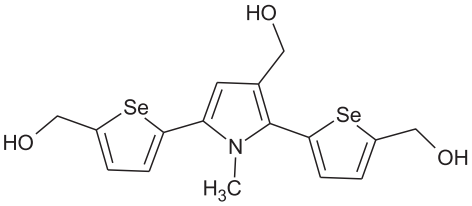
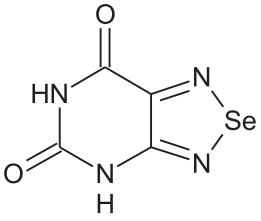
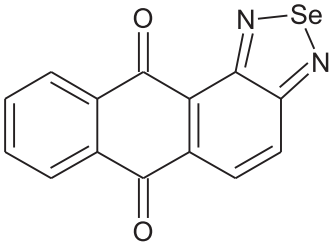
Selenium compounds [CAS number]	Structure	Biological models	Ref.
1,4-Phenylenebis(methylene) selenocyanate, (p-XSC)		*In vitro* Human prostate cancer cells Human oral cancer cells	 [41] [35]
Phenylalkyl isoselenocyanates		*In vitro* Human prostate, breast, colon cancer cells and melanoma, glioblastoma and sarcoma cells *In vivo* Human melanoma	 [68] [68]
2-Phenyl-1,2-benzisoselenazol-3(2H)-one (Ebselen) [60940-34-3]		*In vitro* Human breast cancer cells Human hepatoma cells Human colon cancer cells *In vivo* Human breast carcinoma	 [70] [71] [72] [70]
1,2-[Bis(1,2-benzisoselenazolone-3(2H)-ketone)]ethane (Ethaselen or BBSKE) [217798-39-5]		*In vitro* Human lung cancer cells Human leukemia cells Human prostate cancer cells Human tongue cancer cells Human cervical and gastric cancer cells and hepatoma cells *In vivo* Human breast carcinoma *In vivo combination therapy* Human lung carcinoma (cisplatin)	 [73,78] [74] [75,76] [77] [78] [80] [79]
2,5-Bis(5-hydroxymethyl-2-selenienyl)-3-hydroxymethyl-N-methylpyrrole (D-501036)		*In vitro* Human renal, breast, lung, prostate, colorectal and nasopharyngeal cancer cells Human cervical cancer cells and hepatoma cells	 [81] [81–83]
1,2,5-Selenadiazolo[3,4-d] pyrimidine-5,7(4H,6H)-dione [7698-95-5]		*In vitro* Human breast cancer cells human hepatoma and melanoma cell	 [84]
Anthrax[1,2-c][1,2,5] selenadiazolo-6,11-dione		*In vitro* Human breast cancer cells	 [85]

Table 1 *(continued)*

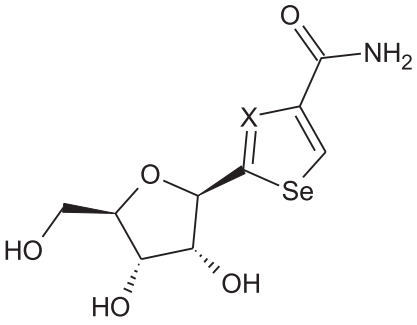
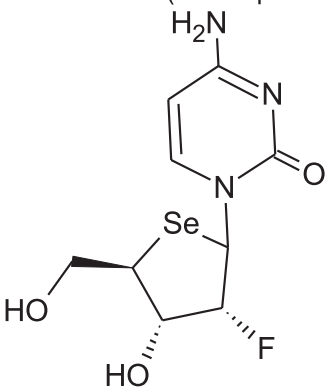
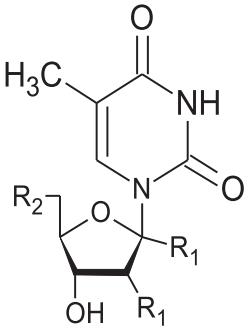
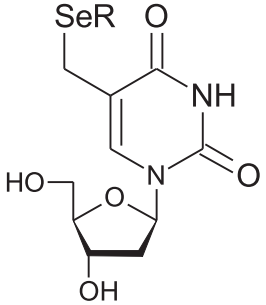
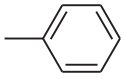
Selenium compounds [CAS number]	Structure	Biological models	Ref.
2-β-N-ribofuranosylselenazole-4-carboxamide (Selenazofurin) [83705-13-9] and 5-β-D-Ribofuranosylselenophene-3-carboxamide (Selenophenfurin) [189145-39-9]	 X = N (Selenazofurin) X = CH (Selenophenfurin)	*In vitro* Mouse leukemia cells [86] Human colon, cervical, renal, bladder cancer cells and lymphoma cells [88] *In vivo* Mouse lung carcinoma [86]	
2′-Deoxy-2′-fluoro-4′-selenoarabinofuranosyl-cytosine		*In vitro* Human colon, lung, stomach cancer, breast, prostate cancer cells and leukemia cells	[89]
Se-thymidine nucleosides	 R_1 = H, $SeCH_3$ R_2 = OH, $SeCH_3$	*In vitro* Human prostate cancer cells	[90]
Se-uridine nucleosides	 R = CH_3, 	*In vitro* Human leukemia cells	[91]

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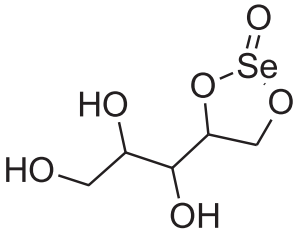
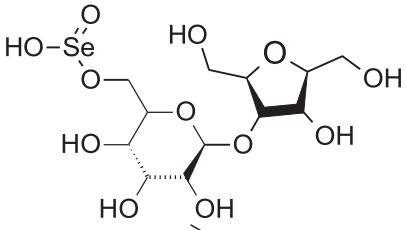
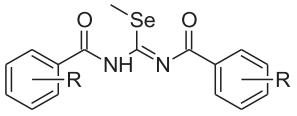
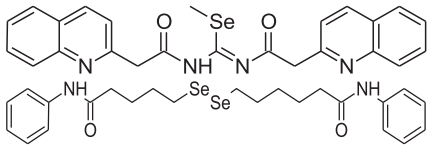
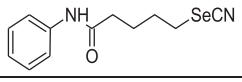
Table 1 *(continued)*

Selenium compounds [CAS number]	Structure	Biological models	Ref.
Xylitol selenious ester		*In vitro* Human liver cancer cells	[92]
Sucrose selenious ester		*In vitro* Human liver cancer cells Human cervical, bladder, gastric cancer cells and melanoma cells	[92] [93]
Quinolinimidoselenocarbamate and imidoselenocarbamate	 R = 3,5-diOCH$_3$, 4-CN	*In vitro* Human prostate cancer cells Human colon and breast cancer cells *In vivo* Human prostate carcinoma	[94,95] [94] [94]
Suberoylanilide hydroxamic acid (SAHA) selenium compounds	 	*In vitro* Human lung cancer cells	[96]

human oral squamous, colon and breast carcinoma cells [39,44,45]. Despite this documented cell killing ability, in the last years MSC has greatly attracted researcher attention thanks to its ability to modulate cellular processes relevant to metastatic processes. The antiangiogenic effects of MSC result in tumor growth inhibition, vascular maturation and enhanced anticancer drug delivery of classical chemotherapeutic drugs, thus leading to an excellent therapeutic synergy in vivo [46,47]. Notably, MSC enhances antitumor activities of irinotecan and tamoxifen in a dose-dependent manner and protects from their toxicity [48–50]. Similar effects were seen cisplatin and oxaliplatin in a variety of drug sensitive and resistant human tumor xenografts [48].

3.2.3. Methylseleninic acid

Many studies reported on the anticancer effects of the oxo-selenium compound methylseleninic acid (MSA) [51]. Its cytotoxic efficacy has been determined in human lung [52], prostate [53–56] and breast [5] tumor cell models and in a mouse mammary epithelial tumor cell line [57]. Moreover, in two prostate tumor xenograft models MSA, was found to considerably reduce tumor growth without inducing substantial animal weight loss or other signs of systemic toxicity nor any evidence of genotoxic side effects [53,58]. In combination therapy, MSA resulted in an enhancement of paclitaxel efficacy for the treatment of triple-negative breast cancer [59].

3.2.4. Selenides and diselenides

Selenocystine, a diselenide oxidation product of Sec, recently gained substantial attention owing to its significant anticancer activity and great selectivity between human cancer cells and normal cells [60]. In in vitro assays, selenocystine has been shown to be effective against human melanoma, cervical and lung cancer cells [36,40,61]. In combination therapy, selenocystine potentiates cancer cell death induced by 5-FU against melanoma cells [62]. Selenocystine also demonstrated potent in vivo anticancer activities in nude xenograft mouse models, by significantly inhibiting tumor growth with no effect on animal weight [61,63]. Even though selenocystine retains a higher antitumor activity compared to SeMet, the poor stability and low solubility of selenocystine strongly hinder its effectiveness and further development as an anticancer drug.

Many other examples of selenides have been tested as antiproliferative agents. Moreno and co-workers have synthesized and tested a series of quinazoline and pyrido[2,3-d]pyrimidine selenium compounds, some of them demonstrating a significant cytotoxicity against a range of human cell cancer lines at low micromolar concentrations [64]. The same authors highlighted a very promising activity of bis(4-aminophenyl)diselenide against lymphocytic leukemia cells [65]. In fact, diphenyl diselenide $(C_6H_5Se)_2$, and its substituted structures have been extensively evaluated for their cytotoxic potential against several cancer cell lines [66,67] and many of these compounds have shown a promising in vitro anticancer activity.

3.2.5. Selenocyanates

Among Se compounds, organic selenocyanates have emerged as a promising candidate during the last years. The first selenocyanate described was the 1,4-phenylenebis(methylene)selenocyanate (p-XSC), that proved to be effective against prostate and oral carcinoma cells [35,41]. Later on, phenylalkyl isoselenocyanates, the isosteric Se analogs

of naturally occurring phenylalkyl isothiocyanates, have shown to be effective both in vitro, against melanoma, prostate, breast, glioblastoma, sarcoma, and colon cancer cell lines as well as in vivo, inducing a substantial reduction of tumor size in a preclinical melanoma tumor xenograft model with no evidence of systemic toxicity. Interestingly, the structure activity relationship studies concluded that tumor inhibitory effect increased with increasing chain length (probably due to an increase in lipophilicity), where n = 4 was found to be the optimal [68].

3.2.6. Se containing heterocycles

Another class of Se compounds that is gaining increasing attention in recent years is represented by heterocycles containing Se. Among all, Ebselen (2-phenyl-1,2-benzisoselenazol-3(2H)-one) is ostensibly the first and most studied heterocyclic compounds derived from Se. Ebselen was first prepared in 1924 [69] and has been widely studied for its anti-inflammatory anti-oxidant properties. More recently, this heterocyclic organoselenium compound has also been proven to inhibit the cell growth of human breast, colon, and hepatoma cancer cells [70–72]. Noteworthy, is the key role of Se in the molecule, clearly shown by the fact that the sulfur analog is completely inactive. On the other hand, its poor solubility remains a problem for optimal therapeutic development. In order to enhance its solubility and to increase its activity, research has focused on modifications of its structure. On these bases, ethaselen (1,2-[bis(1,2-benzisoselenazolone-3(2H)-ketone)]ethane), also known as BBSKE, has been synthesized and extensively investigated by Deng and co-workers. In both in vitro and in vivo studies, this compound demonstrated a significant anticancer efficacy against a variety of human cancers with a moderate toxicity [73–78].

More recently, ethaselen was tested in vivo in combination with cisplatin (cis-diaminedichloroplatinum II, DDP) in a lung xenograft mouse model. Compared to single drug administration, the combination therapy showed a synergistic reduction of tumor size and no obvious signs of systemic or organ toxicity [79]. Despite its promising activity, the goal of increasing solubility in physiological media was not completely accomplished with BBSKE and many solubility and stability problems still remain. Only the formulation as copolymer micelles performed lately by the group of Liu allowed for an increase in water solubility that ultimately led to a further superior antitumor activity due to a massive accumulation into tumor site [80].

The diselenophene derivative D-501036, 2,5-bis(5-hydroxymethyl-2-selenienyl)-3-hydroxymethyl-N-methylpyrrole, has been recently identified as a novel antineoplastic agent with a broad spectrum of activity against several human cancer cells, with IC_{50} values in the low-micromolar range [81–83]. Remarkably, D-501036 elicits a selective cell killing ability against cancer cells compared to normal cells and seems to be highly effective against tumor cell lines that develop Multidrug Resistance phenotype.

1,2,5-Selenadiazoles are also interesting compounds as medicinal agents. Among all, 1,2,5-Selenadiazolo[3,4-d]pyrimidine-5,7(4H,6H)-dione has shown a broad spectrum of cytotoxicity against different human cancer cells [84], and Anthrax[1,2-c][1,2,5]selenadiazolo-6,11-dione induces time- and dose-dependent cell death in human breast carcinoma cells [85]. Many Se-containing heterocycles based on biomolecules (sugars, nucleosides, steroids, and vitamins) have been developed or isolated from natural products in recent years, owing to the success gained in the 80s by Selenazofurin. The nucleoside Se analog of tiazofurin Selenazofurin (2-β-N-ribofuranosylselenazole-4-carboxamide) was synthesized in 1983 by Srivastava and Robins and showed a pronounced anti-tumor activity towards P388, Lewis lung and Ridgeway osteogenic sarcoma animal tumor models [86]. However, N-substituted derivatives were found completely ineffective, both in in vitro and in vivo assays [87]. Conversely, the replacement of the selenazole ring with a selenophene heterocycle led to the formation of Selenophenfurin derivatives, with antiproliferative potencies strictly comparable to that of Selenazofurin [88]. Among the latest Se-nucleoside developed, 2′-deoxy-2′-fluoro-4′-selenoarabinofuranosyl-cytosine (2′-F-4′-seleno-ara-C) [89], thymidine [90] and uridine Se-nucleosides [91] deserve to be mentioned. Among sugars, sucrose selenious ester and xylitol selenious ester have recently gained substantial attention owing to their efficacy against a panel of different cancer cells without affecting normal fibroblasts [92,93].

3.2.7. Miscellaneus Se compounds

Quinolinimidoselenocarbamate and imidoselenocarbamate have been shown to determine cell death in human prostate cancer cells at low-micromolar concentrations [94,95]. Imidoselenocarbamate, in addition, were effective also against breast cancer and lymphoblastic leukemia cells. Desai et al. have synthesized and studied several Se containing analogs of suberoylanilide hydroxamic acid (SAHA), a well-known HDAC inhibitor. Among the reported compounds, bis(5-phenylcarbamoylpentyl) diselenide and 5-phenylcarbamoylpentyl selenocyanide were found significantly more effective in inducing cytotoxicity towards different lung cancer cell lines than the corresponding parent hydroxamic acid [96,97].

3.3. Nanoparticles

Cancer nanotechnology (a multidisciplinary scientific field merging chemistry, biology, bioengineering and medicine) has raised extraordinary high expectation in oncotherapy in the last two decades. Nanoparticles of both metallic and non-metallic origin are under research and development for applications in various nanomedicine fields. Selenium-containing nanoparticles (SeNPs) have recently garnered a great deal of attention as potential cancer therapeutic payloads, due to their excellent biological activities and low toxicity [98,99]. Abundant evidence actually supports the better biocompatibility and bioefficacy of SeNPs when comparing to inorganic and organic Se compounds. A plethora of SeNPs has been developed in the last decade with the aim of obtaining new Se-based therapeutics and theranostics. Non-functionalized SeNPs, synthesized by means of different green chemical and biotechnological procedures, proved to be efficient against a great variety of cancer cells in a dose- and time-dependent manner [100,101]. However, besides the promising antitumor activity elicited by non-functionalized elemental SeNPs, greater attention is growing in the field of surface-decorated SeNPs. Being colloidal systems, SeNPs offer the opportunity of surface functionalization with a variety of different agents, which can be driven to modulate their physicochemical properties, and in vivo pharmacokinetic and biodistribution profiles. Conjugation with functional ligands, indeed, cannot only prevent the aggregation of nanoparticles via plus-to-minus charge interactions, but also enhance the bioactivity of SeNPs.

On these bases, SeNP surface-decorated with ATP [102], AAs [98], *Spirulina* [103] or *Undaria pinnatifida* [104] polysaccharides, *Polyporus rhinocerus* polysaccharides [105], transferrin [106], sialic acid [107], chitosan [108], and folate [109] have been developed. The rationale behind this conjugation is the ability of decorating ligand to target membrane receptors/transporters that are overexpressed on cancer cell plasma membrane. Almost all of the tested surface-functionalized SeNPs were endowed with a superior cancer cell uptake and an improved antiproliferative efficacy with respect to elemental “nude” SeNPs. Based on this, some authors suggest that conjugated-SeNPs might have potential application as chemotherapeutic agents for the management of human cancers. However, at present no in vivo studies have been performed in order to assess the effective bioavailability and pharmacodynamic profile of these SeNP systems that could concretely prove their efficacy in an animal cancer model.

4. Selenium metabolism

The metabolic pathways between different selenium compounds differ significantly and can produce various selenium metabolites

(Fig. 2). This becomes particularly relevant when exploring selenium compounds in treatment of various diseases, as the biological activities of the selenium compounds are mainly exerted via their metabolites and thus determines the efficacy of the compound use. To this extent, a brief overview of the selenium metabolism, with the most extensively studied compounds, is discussed below, but more comprehensive reviews are available [110–112]. These compounds, which are also dietary compounds, include selenate, selenite, SeMet, selenocystine, MSC and γ-glutamyl-selenomethyl-selenocysteine among others. In addition to the naturally occurring forms, there are also several synthetically produced used in supplementation (e.g. MSA).

Selenide is the key metabolite, as all dietary selenium compounds have the ability to directly or indirectly form this common Se intermediate. It is directly formed from inorganic selenite or SDG, through reduction by thiols. It can also be formed through demethylation of methylselenol (CH_3SeH) via methyltransferases or be released from Sec through β-lyase. The reduction of selenate, selenite and SDG can all be facilitated by GSH or the Trx or the glutaredoxin (Grx) systems [113,114]. Noteworthy, are the changes in chemical properties of oxidized glutathione (GSSG) by the insertion of a selenium atom into the molecule to produce GS-Se-SG (or SDG). Normally, GSSG is not a substrate for the mammalian TrxR, whereas SDG has been shown to be an excellent substrate [114]. Even the reduction of SDG by Trx is dramatically altered compared to GSSG. Furthermore, even though GSH is able to reduce these three selenium forms (selenate, selenite and SDG), addition of Grx to the reaction mixture, greatly facilitates the reaction rate [113].

Selenide is also required for selenoprotein synthesis. The selenide formed during metabolism, may then be further converted to selenophosphate, which in turn can react with tRNA-bound serinyl residues to give Sec-bound tRNA from which Sec can be inserted. Sec insertion into selenoproteins is dictated by the UGA codon, and instead of termination of translation, requires the presence of several specific elements such as the conserved stem–loop structure, known as the Sec insertion sequence (SECIS) element [115]. In eukaryotes, the SECIS element is located in the 3′-UTR [1]. SeMet, Sec and CH_3SeH can also be metabolized for the use in selenoprotein synthesis. For this purpose, SeMet needs to be trans-selenated to Sec (in analogy with the trans-sulfuration pathway). Sec, either from this source or directly from the diet, can then be converted to selenide by β-lyase (also known as S-conjugated β-lyase), or produced through the reduction of selenocystine, which is a substrate for TrxR, and the Trx and Grx systems [113,116]. Methylselenol can be demethylated to selenide in an equilibrium reaction for further conversion to selenophosphate. SeMet can in vitro also undergo methylation catalyzed by a γ-lyase to yield methylselenol, but this has however not been detected in vivo [117]. It is thus very likely that SeMet almost entirely is incorporated into selenoproteins, while the alternative γ-lyase pathway only has a minor role. Methylselenol can in turn be formed via cleavage of MSC (or through other Sec-conjugates) by selenocysteine Se-conjugated β-lyase or through the reduction of MSA. Excessive amount of selenide or methylselenol can however be deleterious to the cell, as these forms readily oxidize and can lead to the production of superoxide and other reactive oxygen species with add-on toxic effects [118,119]. Importantly, monomethylated selenium compounds, are direct precursors of putative active anticancer metabolite methylselenol [113]. The relative ability to produce this metabolite should be readily considered in the development of new selenium compounds for cancer therapy. Despite in vitro studies showing higher antiproliferative activity of MSA compared to SeMet and MSC, it retains a similar efficacy profile as MSC in vivo [120]. However, the efficacy of MSC is entirely dependent on the β-lyase activity in organs/tissues, which can vary to a great extent, in order to generate the active methylselenol metabolite [121,122].

There are two distinct pathways for excretion of Se: either through selenosugars (most frequently as 1b-methylseleno-Nacetyl-D-galactosamine) that is excreted in urine, or by the methylation pathway where methylation of CH_3SeH to dimethyl selenide is exhaled while breathing, and trimethyl selenonium ion is excreted in urine. The biological relevance of the selenosugars in not clear, but methylation is considered a detoxification pathway [123,124]. Recent reports of novel selenium compounds that have been identified include selenoneine, originally discovered in fish, but lately also found in human blood along with its

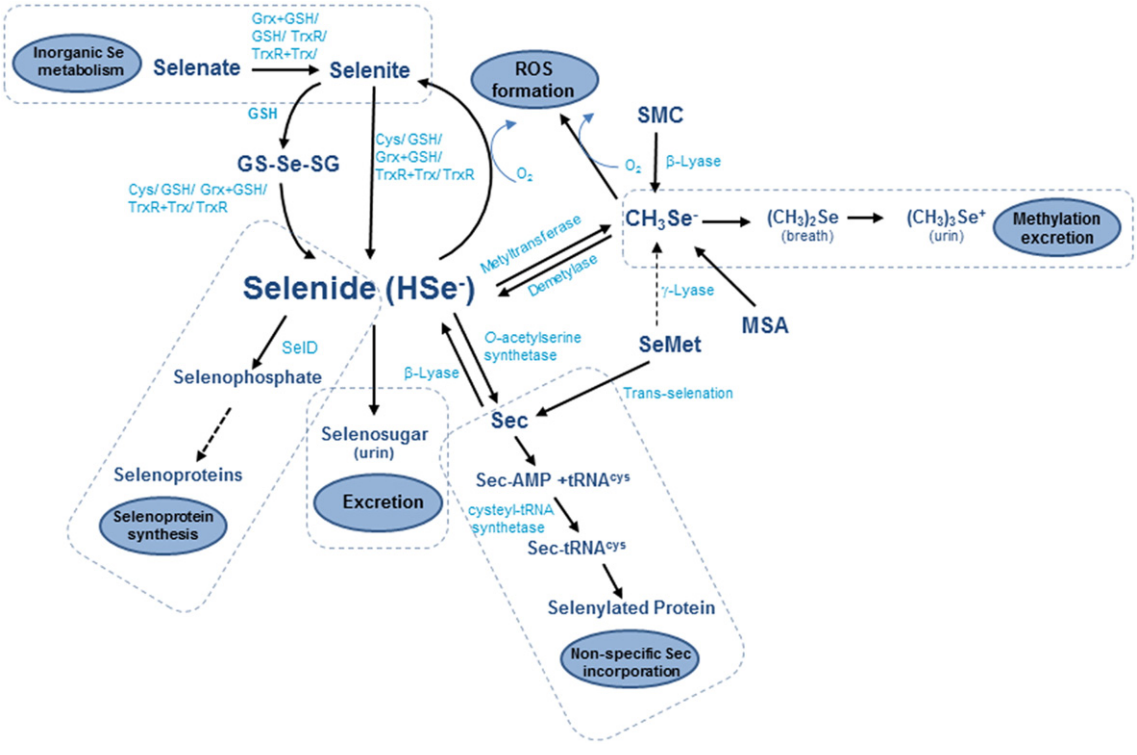


Fig. 2. A schematic overview of the selenium metabolism of the most extensively studied selenium compounds.

novel methylated metabolite Se-methylselenoneine [125]. In terms of novel Se containing anticancer agents, it is vital, not the least from a pharmacological point of view, to elucidate their metabolic pathways in order to understand the fate of the active metabolite, where it accumulates and how it is secreted/detoxified.

5. Selenium and mechanisms of action in cancer cells

The mechanism behind the mediated cell death is diverse, and as previously mentioned it is widely recognized that the effectiveness of selenium compounds as cancer agents is dependent on the chemical form and dose, as well as on redox state and experimental model [5]. There is emerging evidence that cell death by selenium compounds is associated with alterations in uptake, protein modification (including activation/inactivation of signaling molecules and transcription factors), ROS formation, cell growth arrest, induction of programed cell deaths, anti-angiogenic effects and accumulation of misfolded proteins. Selenium compounds may moreover induce cell death by distinct and diverse pathways depending on chemical form and system studied, and include apoptosis (either caspase dependent and independent), necrosis, necroptosis, ER-stress, and autophagy, although autophagy might eventually be a mechanism of resistance rather than cell death. Mechanisms of actions of selenium compounds are discussed below and summarized in Fig. 3.

5.1. Selenium uptake

One of the mechanisms behind Se tumor specificity has been suggested to be attributed to the selective uptake of Se in tumor cells. The first evidence of a selective uptake in tumors was first shown in studies in the 60s where ^{75}Se-sodium selenite and ^{75}Se-SeMet were assessed as scanning agents in the diagnosis of tumors. Through the use of ^{75}Se as a tumor radiotracer, a high accuracy in localizing intracranial tumors as well as thoracic and abdominal neoplasms was observed [126–129]. The mechanism behind selenium uptake is, however, not fully understood, and varies between compounds. Selenide has been suggested to be transported via ATPases [130], while selenite uptake has been reported to be via anion transporters, as hypothesized by Galanter et al. [131], and later demonstrated by the use of 4,40-diisothiocyanatostilbene-2,20-disulfonic (DIDS), an inhibitor of anion transporters [130,132]. The uptake of selenite in cell lines has further been shown to be facilitated by the presence of reducing thiols, indicating that the reduced form is more readily taken up [130]. It was later shown that the accumulation in tumors partly could be explained by the overexpression of the cystine/glutamate antiporter xCT observed in several tumors [133], generating a more reducing extracellular microenvironment, and thus facilitating the uptake of a reduced form of selenium, presumably selenide [134].

5.2. Stress response and cellular targets

As mentioned above, the redox active Se metabolites have proven to be superior as anticancer agents. These compounds have the ability to generate ROS, mainly through redox cycling of selenolates with GSH or the Trx/Grx systems and oxygen to produce superoxide and hydrogen peroxide, and thereby generating oxidative stress and a ROS promoting cellular stress response. As a consequence of the increased ROS formation, as well as by direct interaction and binding, redox active selenium compounds are also known to cause DNA damage and an altered DNA response [36,135–138]. These redox active metabolites have been shown to cause both single and double strand brakes [139]. In addition, selenium compounds may also, by direct interaction with free thiols, cause thiol oxidation. These modifications, which result in the formation of intra- or intermolecular bonds, include the formation of selenotrisulfide bonds (S–Se–S), selenenylsulfide bonds (Se–S), and diselenide bonds (Se–Se) with protein selenols [140]. The redox active selenium compounds may also catalyze the formation of disulfide bonds (S–S) and/or mixed disulfide bonds with glutathione (S–SG) or nitric oxide (S–NO).

Oxidation of structural Cys or Sec residues leading to thiol modification in proteins, consequently results in numerous biological downstream effects, as oxidation of thiols may directly affect the protein structure, biological function or enzyme activity of proteins. Direct modification and regulation of signaling proteins through thiol oxidation include protein kinases, phosphatases, and transcription factors (e.g. the nuclear factor kappaB (NF-κB) and Jun N-terminal kinase (JNK)-signaling pathways) [141]. The best characterized among these are caspases, p53, Jun, AP-1, APE-1/Ref-1, Sp1, NF-κB, ASK-1 and JNK [142–145]. The functions of many of these proteins are in turn regulated through thiol modification by the Grx and/or the Trx systems [146,147]. Furthermore, modifications of critical thiol residues may also result in an altered iron–sulfur cluster biogenesis [148], as well as changes in iron and calcium homeostasis [149–151]. There is also a significant amount of work on selenium compounds demonstrating their interaction with proteins containing zinc-thiolate coordination sites (e.g. metallothioneins) [152–154]. In the presence of GSH the selenium compounds are able to catalyze the release of zinc from these proteins. Selenium compounds

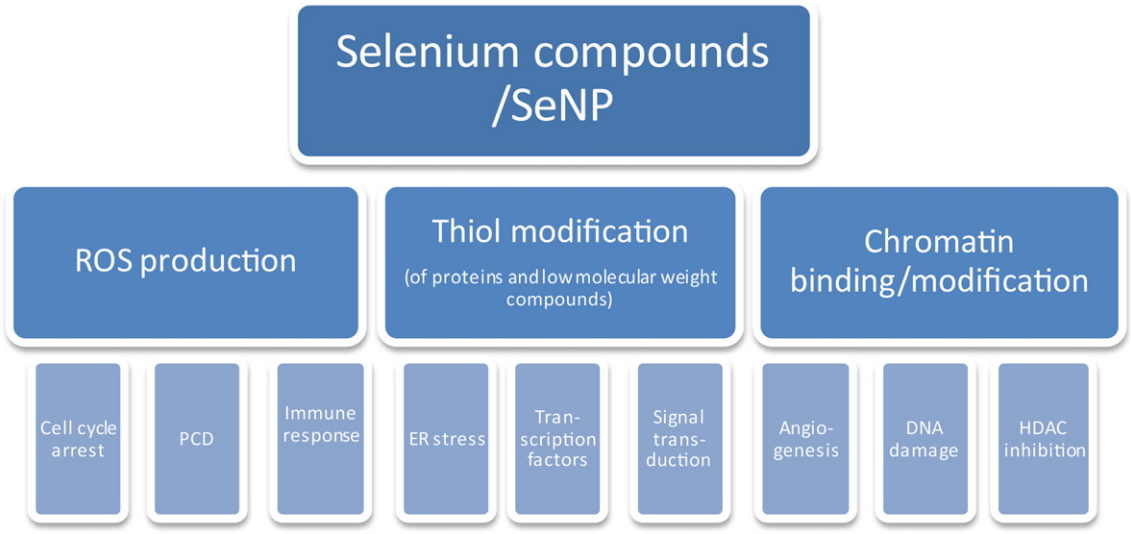


Fig. 3. Illustration of the pro-oxidative effects and downstream targets of selenium compounds.

are also capable of releasing zinc from Cys-rich zinc finger proteins (e.g. transcription factor IIIA and Sp1) and thereby inhibiting their DNA-binding activity [155–157].

Redox modification of thiol/disulfide exchange in proteins by Se may ultimately also lead to protein unfolding. The unfolding of proteins by selenium compounds can either be a consequence of the aforementioned thiol modifications, but presumably also due to unspecific misincorporation of Sec into proteins in place of Cys [158]. This may occur during high levels of intracellular Sec, when a $tRNA^{cys}$ inadvertently binds to Sec instead of Cys during translation to form nonspecific selenoproteins (selenylated proteins), which in turn can result in misfolded proteins with altered structures and biological functions/activities [158,159]. When this occurs, the endoplasmic reticulum (ER) orchestrates a process known as unfolded protein response (UPR) for cell survival. PERK, ATFalpha and XBP1 are three UPR transducer pathways that are all rapidly upregulated when exposed to MSA [160,161]. Moreover, the ER stress markers CHOP and PERK are also altered by MSA exposure. Selenocystine treatment also results in a clear ER stress with effects on the UPR markers CHOP, Bim, ERdj5 and Bip [36]. A few studies have also reported that selenium compounds may result in heat shock response. One group has shown that selenite downregulates heat shock protein 90 (hsp90), which in turn mediates inactivation of NF-κB that switches autophagy to apoptosis in NB4 cells [162].

5.3. Cell signaling pathways

With the mounting evidences of the anticancer potential of selenium compounds, the underlying cell signaling pathways have been explored for a variety of compounds. In a proteomic approach using selenite in promyelocytic leukemia cells (NB4), members of the MAPK family were identified to be affected as were c-myc, c-fos and c-jun that were all downregulated [163]. It has further been suggested that ERK is required and plays an active role in mediating selenite induced cell death in NB4 cells, with slight effects on p38 [164]. Both activation [6,55,56,165,166], or suppression [167] of p38MAP kinase and the JNK have been detected, depending upon the cell type. Similarly, in cervical cancer cells selenite was able to activate p38 pathways affecting other proteins like p21 [168]. Moreover, selenite has been shown to suppress β-catenin and COX2 [166,169]. The effect on β-catenin is exerted by the inhibition of Akt, and the suppression of β-catenin in turn affects its downstream targets cyclin D1 and surviving [169]. The same authors later demonstrated that the inhibition of Akt was via PI3k that caused nuclear accumulation of FoxO3a, which in turn facilitated the transcription of the targeted genes Bim and PTEN in colorectal cancer (CRC) [28]. The organic selenium compounds SDG, in human oral squamous carcinoma cells has been shown to affect stress pathway kinases, JNK and p38 kinase as well as activate ERKs 1&2 and Akt [35]. MSC like selenite has been reported to inhibit the activity of PI3k, following dephosphorylation of Akt and p38. In parallel, MSC may inhibit the Raf/MEK/ERK signaling pathway [170]. Likewise, methylselenol inhibits the ERK1/2 pathway activation and c-myc expression [171,172]. Interestingly, methylselenol has shown to exhibit a stronger inhibition of the cell signaling in the colon cancer (HCT-116) cells compared with the noncancerous (NCM460) cells [171]. MSA has in prostate cancer cells caused a decrease in pAkt and pERK1/2, but here the effects were not mediated by p38MAPK and JNK1/2 [56]. In addition, MSA has been shown to hamper the estrogen receptor (ER) signaling by downregulating ERalpha, highly involved in breast cancer [173].

Despite the fact that selenium compounds like MSA show similar patterns as selenite, with dephosphorylation of Akt and involvement of PI3k, ERK1/2, and p38 [174–176], clear differences have been observed. When comparing the effects of the androgen receptor (AR) expression, which is highly connected to prostate cancer, it was reported that even though both selenite and MSA could disrupt AR signaling, they had distinct mechanisms of action. Selenite decreased the levels of Sp1 known to regulate AR expression, while MSA did not [145]. While MSA, selenite, SDG and selenocystine have all been shown to catalyze the oxidation of active site Cys thiols in protein kinase C, only SDG and selenocystine were capable of inhibiting protein kinase A [177–179]. Selenate on the other hand, has been associated with the suppression of mTOR via Akt dependent and independent mechanisms in colon cancer cells [180]. Dysregulation of mTOR has also been observed for MSA via induction of REDD1 and Akt, in prostate cancer cells grown under hypoxic conditions [181].

Differences between selenium compounds as kinase modulators have also been investigated using a library comprising of organoselenium compounds [95]. In the specific study, the authors registered interesting differences between the structural subsets within the library. Generally, one can say that the symmetric compounds with an imidoselenocarbamate moiety exhibited the broadest inhibitory effect on the tested kinases, while selenylacitic acids and selenodiazoles in contrast, did not inhibit kinase activity at all [95].

5.4. Cell cycle arrest and programed cell death pathways

A myriad of studies have proven, in diverse cancer cell lines, the effects of selenium compounds on cell cycle arrest and the cell death pathways involved. However, as mentioned above, the mediated cell cycle arrest and cell death mechanism vary depending on selenium compounds and on cell phenotype (summarized in Fig. 4).

Selenite has been shown to induce different cell death pathways, including apoptosis, necroptosis, necrosis and autophagy. Many authors have demonstrated that selenite treatment determined morphological signs of apoptosis [21,182–187], but the regulating mechanisms of selenite induced apoptosis look very complex. In a murine melanoma C57BL/6 mouse model [188], in human prostate [165,187], and lung [189] cancer cell lines as well as in leukemia [29] cells, apoptosis was caused through arrest of cell cycle distribution at sub-G1/G1 stage. On the other hand, diverse papers have reported the ability of selenite to block cell cycle at S or G2/M phases, determining a concomitant increase of cells in sub-G1 phase [17,20,26,30,44,56,136,190,191]. Many reports converge in asserting that selenite induces p53-dependent apoptosis [44,192–195]. Concerning caspase involvement, in human prostate [56], cervical [168] and lung [23] cancer cells, selenite exposure triggered a caspase-independent apoptosis, whereas a caspase-dependent pathway was detected in lung [167], mesothelioma [6], osteosarcoma [196], colon [44] cancer cells and in leukemia cells [192]. In many cancer cells, Bax was up-regulated and Bcl-2 was down-regulated after sodium selenite treatment [6,17,20,26,189,197]. Accordingly, mitochondrial-related apoptosis, revealed by cytochrome c release and mitochondrial membrane potential loss, was detected in many different cancer cell lines subjected to selenite treatment [6,14,17,26,30,31,54,186,189,197–199]. Conversely, only few papers have reported the induction of necrosis by selenite treatment [200–202]. Recently, we highlighted a partial inhibition of cell death by necrostatin-1 in cervical cancer cells, suggesting the involvement of necroptosis, rather than necrosis, in selenite-induced cell death [36]. Several studies have reported that sodium selenite induced autophagy in cancer cells. However, the role played by sodium selenite-induced autophagy in cell death has been disputed. Kim et al. reported that selenite triggered superoxide-mediated autophagic cell death in glioma cells [199,203]. On the other hand, it has been also shown that sodium selenite-induced autophagy functioned as a survival mechanism in leukemia [204] and lung cancer cells [189].

Inorganic selenate has been shown to induce apoptosis in leukemia and hepatoma cells involving the down-regulation of Bcl-2 and up-regulation of p53 [205]. Moreover, Takahashi et al. showed that selenate induced apoptosis in human oral squamous carcinoma cells [31]. Remarkably, selenium dioxide has been proven to effectively enhance lymphocyte progression into the S-phase of the cell cycle in patients with stage IV cancer, thus restoring immune function and controlling cancer progression [206].

Fig. 4. Summary of the known mode of programmed cell death generated by selenium compounds.

Concerning organic selenium compounds, SeMet has been shown to induce apoptosis by both causing G0/G1 [165] or G2/M phase arrest [165,207–209]. Apoptosis caused by SeMet, has been shown to be both p53-dependent [39,208] and independent [210], and correlated with an increase in ERK phosphorylation [211] and PARP cleavage [165]. As regards to SDG, Lanfear and co-workers underlined that it can induce cell death by an apoptotic pathway in a p53-independent manner [33]. The methylated selenium form MSC has been shown to induce apoptosis in several model systems. Notably, it has been shown to induce apoptosis by cell growth arrest in S phase in a mouse mammary epithelial tumor cell model [212]. Moreover, MSC activated apoptosis cell death by increasing caspase activities in human promyelocytic leukemia cells as well as in ovarian and oral squamous tumor cells [39, 213–215]. Even though no release of cytochrome c was detected in MSC-treated ovarian cancer cells, MSC caused a cytochrome c accumulation in time- and dose-dependent manner in the cytosol of human leukemia cells, thus suggesting that its apoptotic effect in this latter phenotype is mitochondrial-dependent [213]. Similarly, MSA has been shown to induce apoptosis in different cancer cell lines. Against prostate cancer cells, MSA treatment resulted in a G(1) arrest, with reduction of cyclin D1 and induction of the cyclin-dependent kinase-inhibitory proteins p27kip1 and p21cip1 [56,216,217]. Notably, MSA induced apoptosis either in p53 wild-type [54], p53-mutant [55] and in p53-null cells [161], thus attesting to act by a p53-independent way. MSA-induced apoptosis was accompanied by the activation of multiple caspases (caspase-3, -7, -8 and -9), cytochrome c release and PARP cleavage [55,56].

Selenocystine has been shown to trigger a p53- and caspase-dependent apoptosis pathway in human melanoma and breast cancer cells [61,63]. In particular, PARP cleavage, activation of multiple caspases (-3, -7, -9, -8, -10), release of cytochrome c, apoptosis-inducing factor (AIF) and Smac/Diablo from mitochondria to the cytosol and truncation of Bid were distinctive signs of selenocystine-induced apoptosis in human melanoma cells, thus indicating the activation of both intrinsic and extrinsic apoptosis. Besides the expression of Bclxl, Mcl-1, Bad, Bik and Bok was not affected by selenocystine treatment,

the expression level of Bcl-2 was significantly decreased and those of Bax and PUMA-α were slightly increased. On the other hand, the same authors reported that selenocystine determined caspase-independent apoptosis in human MCF-7 breast cancer cells [63]. Moreover, we have recently demonstrated that in cervical cancer cells selenocystine induced both paraptosis and apoptosis-like cell death, the latter being accompanied by induction of BIM and caspase-3 cleavage [36]. On the contrary, little is known about the mechanism of cell death induction by other selenides. Only recently, Posser et al. showed that diphenyl diselenide was able to induce apoptosis in human neuroblastoma cells by the ERK1/2 pathway [66] and, likewise, Nedel and co-workers showed that other diselenides caused apoptosis by inducing G2/M cell cycle arrest as well as caspase and p53 activation [67].

Selenocyanate derivatives have been shown to induce apoptosis in human cancer cells by decreasing Akt phosphorylation [65,218–221]. In particular, similarly to that observed for SDG, against human oral squamous carcinoma cells, p-XSC induced JNK and p38 kinase, and activated ERKs 1&2 and Akt [35]. Furthermore, p-XSC-mediated apoptosis was proven not to be dependent on p53 expression in human colon cancer cells [222].

Among Se heterocycles, Ebselen has shown to cause a dose- and time-dependent loss of mitochondrial membrane potential and release of cytochrome c in human hepatoma cells, but the apoptosis induction was caspase-independent [223]. Conversely, its structurally related derivative BBSKE inhibited tongue cancer cell growth by promoting apoptosis through the activation of caspase-3 [77]. Juang and co-workers showed, in addition, that selenophene derivative D-501036 determined cell death in both hepatic and renal carcinoma cells through a dose-dependent accumulation in S phase with concomitant loss of both the G0/G1 and G2/M phase [81]. Later, the same authors denoted that D-501036-induced apoptosis was caspase dependent, as attested by its ability to increase of the activities of caspase-9 and -3 in a dose and time dependent manner [82].

Apoptosis was the main cell death mechanism triggered by either Se-nucleosides or Se-sugars. Kim et al. reported that uridine Se-nucleosides induced apoptosis in human cancer cells involving p38 pathway, caspase-2 and -3 and, to a lesser extent, caspase-8 and -9 [91,224]. Guo et al., in addition, highlighted that xylitol-Se and sucrose-Se induced mitochondrial apoptosis by depletion of mitochondrial membrane potential and activation of caspase-3 in liver cancer cells [92].

Despite that the SeNP field has been receiving increasing attention, at present very little is known about the mechanism by which SeNP exerted their antiproliferative activity. Even though cell death mechanism seems to be strongly affected by surface SeNP functionalizing molecules, apoptosis has been reported to be the principal cell death pathway [100,103,104,225]. Kong and collaborators reported that SeNP inhibits prostate cancer cell growth partially by caspase-mediated apoptosis, which was through activation of the Akt/Mdm2 pathway [225]. SeNP functionalized with *U. pinnatifida* polysaccharides induced apoptosis in human melanoma cells through mitochondria-mediated pathways [104].

5.5. Epigenetic effects of selenium compounds

A few relatively recent studies have also connected the chemotherapeutic effects of selenium compounds to inhibition of histone deacetylases (HDACs). HDACs are involved in the regulation of gene expression and are promising anti-cancer targets, being upregulated in many cancers. α-Keto-γ-methylselenobutyrate (KMSB) and β-methylselenopyruvate (MSP) resemble short chain fatty acid inhibitors of HDACs, and are formed during the transamination reactions of SeMet and SMC. Both KMSB and MSP have in vitro been shown to act as competitive inhibitors of HDAC [226,227]. These metabolites are however only formed in cells where the transaminases are active. MSA has also been suggested to inhibit HDAC activity in diffuse large B-cell lymphoma cell lines [228], as well as in esophageal squamous cell carcinoma [229]. In the latter, an induction of acetylation of histone H3 at Lys9 was observed. Selenite in accordance with MSA has also shown to increase the levels of acetylated lysine 9 on histone H3 and to decrease levels of methylated H3-Lys 9 in prostate cancer cells [230]. In the same study, a general decrease of histone deacetylase activity and DNA methylation was also observed. In breast cancer distinct effects have been observed for MSA and selenite, where MSA was shown to decrease H3K9me3 and increase H4K16ac, while selenite decreased the latter histone mark [231]. The suggested mechanism behind the effects of selenite and MSA is believed to be through oxidation of conserved Cys residues, known to disrupt the activity of class I HDACs [228,232], and therefore differs from the underlying mechanism of SeMet and SMC. Selenium compounds may thus have two distinct mechanisms of HDAC inhibition.

6. Selenium in angiogenesis and metastasis processes

Angiogenesis, defined as the formation of microvessels from existing vessels, is a vital and mandatory step in solid tumor development and metastasis. There is growing and supporting evidence that Se may regulate vascularization and that the effects may depend on the selenium compounds used. For instance, downregulation of the mRNA levels of matrix metalloproteases (MMP-2, 9, 14, 15, 16, 24), tissue inhibitors of metalloproteinases (TIMPs) and epidermal growth factor receptor (EGFR) after selenite treatment has been observed in low-passage culture of biopsy derived glioma cells (IPSB-18) [9]. Others have reported similar findings where selenite caused increased loss of MMP in colon cancer cells [17]. MSA has also shown to cause a decrease of the secretion and protein expression of MMP-2 and TIMP-1 [233,234]. This has been suggested to occur via inhibition of pro-MMP-2 activation mediated by suppression of MT1-MMP expression, which in turn is mediated through suppression of the NF-κB activity [235]. The active form of MMP-2 has also been decreased in HT1080 cells after treatment with methylselenol. In the same study, methylselenol increased the protein levels of TIMP-1 and TIMP-2 [236].

Vascular endothelial growth factor (VEGF) is a central protein in angiogenesis, stimulating the formation of new blood vessels. Selenite has in many studies been shown to have the potential to inhibit VEGF, and this is further believed to occur in a MAPK-independent manner [234,237]. Selenite has also been shown to inhibit LPS-induced expression of TGFβ-1 and VEGF as well as IL-6 in prostate cancer cells [238]. In the same study, an inhibition of the translocation of the NF-κB p65 subunit to the nucleus was also observed. Likewise, MSA treated bone metastatic mammary cancer cells resulted in decreased VEGF levels [239]. MSA also inhibited HIF-1α expression and VEGF secretion in lymphoma cell lines and in prostate cancer cells [228,240]. Selenite-treated melanoma cells do not only inhibit the VEGF expression, but also decrease hypoxia-inducible factor-1α (HIF-1α) and inhibit IL-18 [241]. Treatment of metastatic rat and human prostate cancer cell lines with MSA also decreases HIF-1α levels and reduces VEGF and GLUT1 [240]. In this model, significant decrease in microvascular density, and promotion of vascular normalization was also observed. Consistently, rats supplemented with relative high levels of selenite (3 ppm) exhibited a similar reduction of microvascular density [237]. The effect of microvascular density seems to be quite rapid, with a significant reduction seen after only three days [237]. In accordance with selenite and MSA, MSC has been reported to cause reduction of HIF-α 1 and 2 levels in renal cell carcinoma [242]. CRC xenografts, HCT-8 (uniformly poorly differentiated) and HT-29 (moderately differentiated tumor with avascular glandular regions) have been used to study tumor vasculature. MSC led to a significant tumor growth inhibition, a reduced microvessel density, and a more normalized vasculature in both colorectal xenografts [243]. Other models (human head and neck squamous cell carcinoma xenograft models) have been used to prove the reduced microvessel density and increased vascular maturation by MSC through HIF-1α

and VEGF [49,244]. In telomerase-immortalized microvascular endothelial (TIME) cells, the microvessel density of the tumors in the high MSA treated group was decreased by more than half from the control [245]. In a nude mouse model with hormone refractory prostate cancer, selenite was shown to be the most effective selenium compounds used (compared to SeMet, selenocystine and selenized yeast), with a significant decrease in tumor size, lymph node metastases, and microvascular density [246]. In human umbilical vein endothelial cells (HUVEC), p38 MAPK was shown to be a key upstream mediator for the methylselenol-specific induction of vascular endothelial caspase-dependent apoptosis [247].

In spontaneous metastasis of Lewis lung carcinoma C57BL/6 mice, MSA significantly reduced pulmonary metastatic yield, reduced plasma concentrations of VEGF, fibroblast growth factor basic and platelet-derived growth factor-BB. In a murine melanoma C57BL/6 mouse model the tumor metastasis was suppressed by selenite [188]. Conversely, the non-redox active metabolite, SeMet, did not affect any of the aforementioned measurements [248].

7. Selenium and immune response

Even though a pile of evidence is gathered for the importance of Se for the immune response at nutritional levels, especially in viral immune responses, surprisingly little is still known about the effects of Se on the immune system at higher/chemotherapeutical doses in cancer. One early study in rats demonstrated an increase in NK-cell activity as well as an enhanced NK-cell cytotoxic response [249]. This has been supported by others that have shown that selenium supplementation caused enhanced expression of spontaneous NK-cell cytotoxicity in spleen cells and of specific cytotoxic T-lymphocyte cytotoxicity in peritoneal exudate cells in mice [250]. In a bilayer lipid membrane system Se enhanced the NK-cell cytotoxicity [251]. Supplementation of selenite in a mouse model has also resulted in the formation of significantly higher numbers of high affinity IL-2R/cell [252]. More recently, treatment with selenite on tumor cells resulted in a loss of HLA-E expression, and caused increased susceptibility to CD94/NK group 2A-positive NK cells [253]. The underlying mechanism behind these effects remains largely unclear.

8. Concluding remarks

Selenium compounds are potent anti-proliferative agents, with modest effect on normal tissues and clinically well tolerated. The exact mechanism by which this anti-tumor activity is mediated remains unclear, although numerous mechanisms have been proposed and is distinct depending on compound and system examined. Selenate has, per orally, been shown to be well tolerated at a dose of 60 mg per day, and with modest single-agent efficacy similar to other anti-angiogenic compounds in an open-labeled phase 1 study [254]. Ethaselen is one compound which seems very promising as an anti-tumor and anti-cancer drug, and has now entered phase I clinical trials in China [79]. Further clinical trials are warranted and it is likely that the full potential of selenium compounds as anticancer agents in both solid and hematological cancers will only be realized once novel tumor targeted selenium compounds/SeNP have been developed and tested in clinical trials. It might also require the development of rational combination therapies that can be predicted to have synergistic or additive effects. To this end, understanding the underlying mechanisms of specific selenium compounds is an essential feature.

Acknowledgement

This article has been financially supported by the Swedish Cancer Society (Cancerfonden, grant number: 2013/453) and the University of Padova (Progetto di Ateneo CPDA131114/13).

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