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Wound healing is aided by glutathione peroxidase, a selenoprotein

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Background: A multitude of cellular and molecular pathways are involved in the intricate biological process of wound healing. Particularly important in reducing oxidative stress and facilitating cellular repair are selenoproteins, and more specifically glutathione peroxidases (GPXs). Injuries frequently cause increased reactive oxygen species (ROS), which can lead to oxidative stress and harm cells and slow the healing process. Neutrophils, inflammatory cytokines, and reactive oxygen species (ROS) are essential components of the inflammatory response that starts the repair process. Antioxidant systems like selenoproteins are necessary because excessive ROS can worsen tissue damage. Selenium, a vitamin that is crucial for proper protein function, may also play a therapeutic role in cancer treatment and wound healing.
Aim: The goal of this research is to better understand the antioxidant processes, inflammatory pathway interactions, and therapeutic potential of selenoproteins as they relate to wound healing and oxidative stress-related problems. The usage of selenium-based chemicals to improve recovery and fight linked diseases like cancer is being investigated in the study, as are the consequences of selenium supplementation.

Conclusion: Finally, selenocysteine, methylselenocysteine, and methylseleninic acid are only a few of the selenium compounds that have demonstrated promise as cancer treatments owing to their capacity to trigger cell death and influence important physiological functions. These chemicals have the potential to kill cancer cells by activating caspase pathways, which in turn release cytochrome c and cause DNA damage. Meliselenocysteine and other selenium-based chemicals do not depend on p53 to determine cell death, yet they are nevertheless effective against many different types of cancer cells. With dose-dependent cytotoxicity and normal cell sparing, methylseleninic acid in particular has shown encouraging anticancer effects across several cancer types. Their promise as cancer targeted therapeutics is expanding as more is learned about their action mechanisms and selenium compounds are synthesized better.

Keywords: Wound healing, Selenoproteins, Glutathione peroxidases (GPXs), Reactive oxygen species (ROS)

Introduction

Platelets initiate coagulation and thrombus formation at sites of injury, creating a scaffold for subsequent wound healing. During this process, neutrophils release a variety of reactive oxygen species (ROS), including lipid peroxidases (LP) and hydrogen peroxides (HP), while immune cells

secrete inflammatory cytokines. ROS are naturally occurring molecules essential for cellular communication and homeostasis. However, environmental factors such as heat and ultraviolet radiation can elevate ROS levels, potentially causing oxidative stress and damaging cellular structures. Inflammation triggers the release of matrix metalloproteases (MMPs), HP, metal scavengers, and LP. These factors collectively stimulate NOX2 gene expression in cell plasma membranes. Activation of NOX2 during phagocytosis further drives the production of superoxide radicals, amplifying the oxidative response.[1]

Selenoproteins, particularly glutathione peroxidases (GPXs), play a pivotal role in wound healing. GPXs are antioxidants comprising a group of eight known isoforms, each characterized by distinct chemical compositions, distributions, roles, and mechanisms of action. Five of these isoforms contain a selenocysteine (SeCys) residue in their structure, which facilitates the catalytic processes involving heavy metals, lipids, and hydrogen peroxides.[2]

Glutathione acts as an electron donor, restoring protein cysteine residues in the cytoplasm by converting disulfide bonds. During this process, glutathione is oxidized, forming glutathione disulfide (GSSG), also known as l-(−)-glutathione. Glutathione peroxidases (GPXs) play a crucial role in mitigating oxidative damage by converting hydrogen peroxide into less reactive molecules like water and oxygen. This reaction prevents processes such as the Fenton and Haber-Weiss reactions, which can generate highly reactive hydroxyl radicals. The efficiency of these processes varies depending on the metal involved, as different metals exhibit unique oxygen transport and catalytic properties. GPX1 mRNA expression increases during the inflammatory phase, highlighting its critical role in wound healing.[3]

GPX1 activity decreases after wounding in rats, irrespective of their immunological status. This reduction is attributed to the drop in GPX1 levels during the initial stage of wound healing. Also, selenocysteine activity diminishes following nitric oxide-induced oxidation or alkylation. Similarly, high levels of superoxide dismutase (SOD) and hydrogen peroxide can inactivate selenocysteine, metabolizing it into dehydroalanine.[4]

The availability of selenium directly limits the synthesis of GPX proteins. Selenium deficiency is prevalent among patients with trauma-related wound healing impairments. GPX2 protein levels decrease in low-selenium environments but increase following selenium supplementation. Further research is required to clarify the precise mechanisms involved. Selenium supplementation may be considered as a medicinal intervention when conventional wound healing methods prove ineffective. Figure 1 illustrates the roles of various selenoproteins in wound healing.[5]

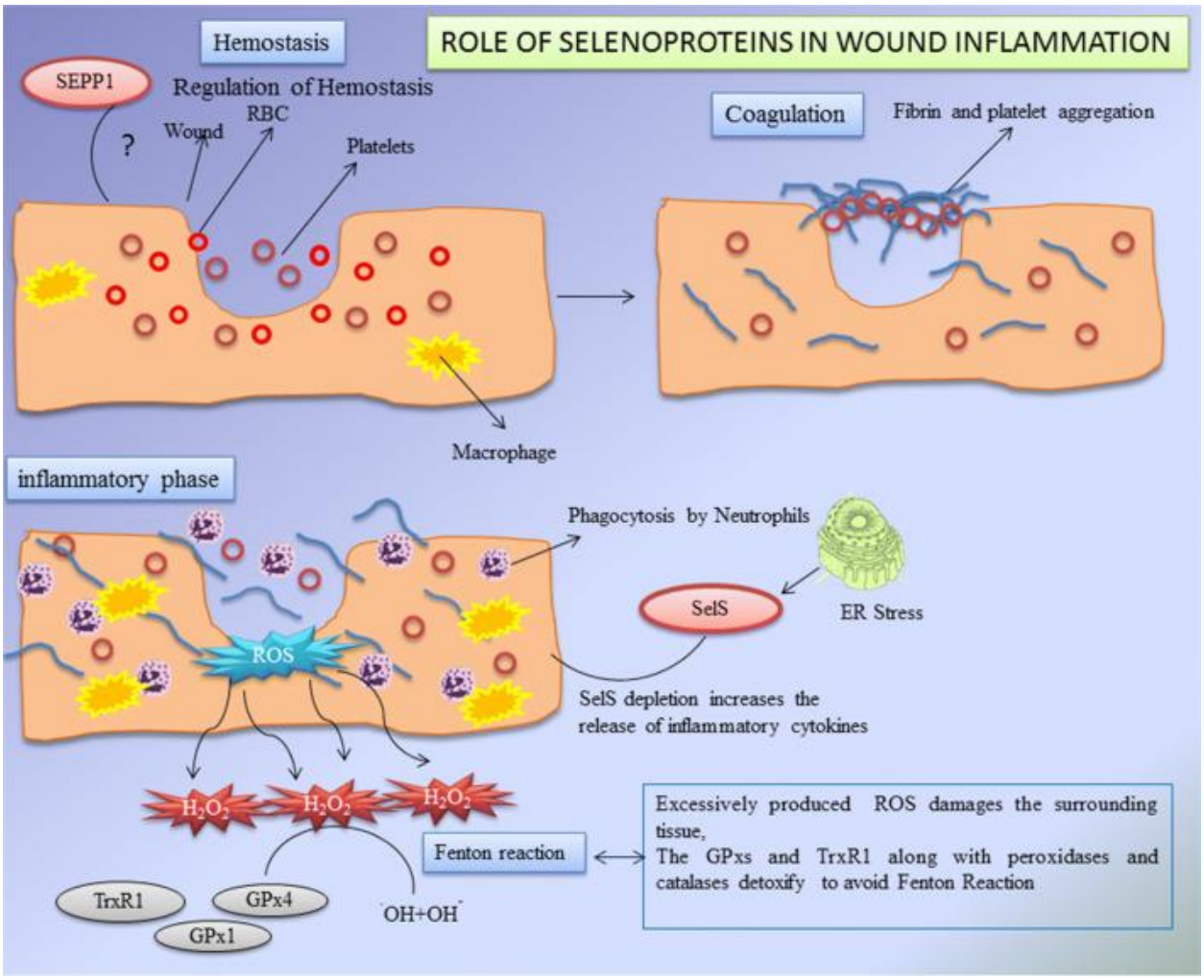

Figure 1: Selenoproteins (GPXs, GPX-Glutathione peroxidases, TrxRs, thioredoxin reductases, SelK, SelS, and SelP) and their roles in wound healing[6]

Healing Wounds with Selenoprotein S

During the inflammatory stage of wound healing, various soluble factors, including chemokines and cytokines, are produced. These agents play a critical role in clearing debris, pathogens, and injured tissues through mechanisms such as phagocytosis. Emerging evidence highlights the essential role of selenoprotein S (Sel S) in the inflammatory process. This transmembrane protein, also known as SELENOS, TANIS, SEPS1, and VIMP, is in both the plasma and endoplasmic reticulum (ER) membranes. Sel S performs three primary functions: protecting cells from oxidative stress, facilitating the clearance of misfolded proteins from the ER lumen, and contributing to cell death induced by ER stress. Initial studies on Sel S were conducted in diabetic rats, using fasting diabetes tests, and established a molecular link between Type 2 diabetes, inflammation, and cardiovascular complications.[7]

Notably, Sel S interacts with Serum Amyloid A (SAA), a key protein involved in the acute-phase inflammatory response. It has been observed that the nuclear factor (NF)-κB pathway activates the ER stress response element to induce Sel S production under conditions of ER stress. Furthermore, research suggests that Sel S plays a role in modulating inflammatory responses and cytokine production in macrophages. Reduction of Sel S expression using siRNA has been shown

to increase the release of inflammatory cytokines, such as IL-6 and TNF-α. These findings underscore the importance of Sel S in regulating inflammation and maintaining cellular homeostasis during stress responses.[8]

A specific polymorphism in the Sel S gene has been linked to increased levels of inflammatory cytokines in the plasma. 105G-A variation in the Sel S gene is associated with numerous inflammatory markers. This suggests a potential connection between Sel S's role in the inflammatory response and the inflammatory phase of wound healing. However, further experimental research is necessary to validate and expand on these assumptions, providing a clearer understanding of Sel S's involvement in inflammation and its broader physiological implications.[9]

Wound healing and the function of supplemental selenoproteins

Catalase enzymes

Thioredoxin reductases (TR1, TR2, and TR3) are three distinct forms of enzymes that play a crucial role in redox signaling and modulating antioxidant activity. TR is primarily involved in these processes. The thioredoxin system regulates the redox state of transcription factors, thereby influencing gene expression. Key proteins in this regulatory process include NF-kB, Ref-1, AP-1, P-53, and the glucocorticoid receptor (ASK-1). These transcription factors are essential in controlling various cellular responses, including inflammation and stress reactions.[10]

One of the critical functions of thioredoxin reductase is its ability to recycle ascorbate, which reduces ascorbyl free radical levels. Ascorbic acid is an important antioxidant that helps protect cells from oxidative stress and inflammatory damage. However, humans cannot synthesize ascorbic acid, making it reliant on external sources. In this context, selenoproteins like thioredoxin reductase play a vital role in wound healing, particularly in processes involving oxidative stress and inflammation, by supporting antioxidant defense mechanisms and promoting cellular repair.[11]

Protein that contains seleniprotein P

Selenoprotein P (Sel P or SEPP1) is unique among selenoproteins due to its structure, containing ten selenocysteine residues, glycosylation in proteins as the presence of three N-glycosylation sites and one O-glycosylation site. The synthesis and transport of selenium to plasma predominantly occur in the liver. Once released into the bloodstream, selenium P is distributed to various organs and tissues. Selenoprotein P is thought to play a critical role in multiple biological functions, including wound healing, normal and abnormal metabolic processes, and regulating hemostatic balance. It also serves as an important carrier for selenium transport throughout the body. However, while the evidence suggests that selenoprotein P is involved in these processes, its precise function during the wound healing process remains to be further investigated.[12]

Using selenium in treatment

Most people obtain their selenium through dietary supplements, as noted by Lau et al. (2017). Selenium is a crucial component of selenoproteins, which are involved in a wide range of cellular functions. These trace amounts of selenium are sufficient to maintain optimal health, as emphasized by Wu et al. (2015). Selenium plays a significant role in regulating thyroid hormone activity, inflammation, redox reactions, reproductive and cardiovascular health, brain function and repair, carbohydrate metabolism, and immune responses.[13]

Selenium deficiency is associated with several health problems, according to Vinceti et al. (2017). On the other hand, excessive selenium intake can lead to selenosis, a toxic condition resulting from selenium poisoning. The current recommended daily intake of selenium is 55 µg (0.7 µmol). Individuals consuming less than 15 µg of selenium per day are at an increased risk of selenium deficiency, while those exceeding 400 µg per day are at risk of selenium toxicity.

However, a study by Vinceti et al. (2001) suggests that the recommended daily intake of selenium may be much lower than previously thought, prompting further reevaluation of selenium's optimal levels for health.[14,15]

Cancer therapy using medicinal selenium compounds

Research into the relationship between selenium and cancer dates to the mid-20th century, with many considering selenium supplements as a potential treatment or preventive measure for cancer. Selenium exists in a variety of forms, both organic and inorganic, and more recently, selenium nanoparticles (SeNPs) have emerged as a promising tool with demonstrated anticancer properties. The anticancer effects of selenium compounds are largely attributed to their antioxidant capabilities. Rahmanto and Davies (2012) explain that these antioxidant properties help maintain intracellular redox balance, protecting healthy cells from oxidative damage caused by reactive oxygen species (ROS).[16]

Reactive oxygen species, which are free radicals, are generated during normal biochemical and physiological processes. However, excessive ROS production can lead to increased oxidative stress and DNA mutations, accelerating carcinogenesis, as highlighted by Prasad et al. (2017). The ability of selenium to modulate ROS levels and protect cells from oxidative damage makes it a potentially valuable compound in cancer prevention and treatment.[17]

At low concentrations, reactive oxygen species (ROS) govern many cellular functions, which is really highly useful, despite its association with cancer. To eliminate harmful microorganisms, certain cells and enzymes produce superoxide radicals, as demonstrated by Georgieva et al. (2017). Reactive oxygen species also promote cellular senescence and death, which damages cells.[18]

Based on the research done on these chemicals, organic and inorganic selenium compounds have distinct metabolic profiles and cancer cell targeting abilities. Humans are better able to absorb and use organic selenium molecules, although inorganic selenium compounds are equally absorbed and used. Numerous studies have shown that selenium compounds, both organic and inorganic, can inhibit the development of cancer. These studies include Brigelius-Flohé and Flohé (2017), Fernandes and Gandin (2015).[19,20]

Nevertheless, selenium compounds have been found to be hazardous. The research indicates that inorganic selenium compounds exhibit a higher level of genotoxic stress. These substances may not be as helpful as first thought, and they may even be more dangerous and increase the chance of cancer growth. Organic selenium compounds, on the other hand, are more effective against cancers, have less side effects, and significantly improve metastasis prevention. Organic selenium compounds are unique among nucleophilic chemical types. Although several factors affect the harmful effects of selenium compounds, the type of compound and the amount of exposure are the most crucial.[21]

Selenium compounds that are not organic

Much research has focused on the inorganic selenium compounds sodium selenite and sodium selenate to determine whether they have any therapeutic effects on cancer. The valence state of these substances determines their actions and behaviors. Over the course of 48 hours, several dosages of sodium selenate and sodium selenite were examined for their capacity to sensitize KB cells, which are human oral squamous carcinoma cells resistant to vincristine. The concentrations of sodium selenate and sodium selenite were 5, 10, 30, and 50 μM, and 0.1, 0.25, and 0.5 μM, respectively. Our careful observation revealed that they sensitize KBV20C with the same efficiency as the sensitive parent KB cells. According to Choi et al. (2015), medicines that

contain sodium selenite are better at sensitizing KBV20C cells because they start cell death pathways and interrupt the cell cycle at G2-phase.[22]

Sodium selenite has garnered significant attention due to its remarkable anticancer and chemopreventive properties, making it the focus of extensive research.[23] Studies have shown that when administered at doses ranging from 5 to 100 μM over 2-5 days, sodium selenite demonstrates potent anti-proliferative effects against several oral cancer cell lines, including HSC-3, HSC-4, and SAS (Endo et al., 2017). Additionally, Tan et al. (2018) discovered that sodium selenite inhibits the proliferation of various cancer cells, including lung cancer, the deadliest form of cancer globally.[24]

Research by Berthier et al. (2017), and Lipinski (2017), further supports these findings, indicating that sodium selenite exhibits a higher sensitivity to lung cancer cells compared to other human cancer cell lines. These results highlight the potential of sodium selenite as a promising therapeutic agent in cancer treatment, particularly for lung cancer.[25,26]

Previous studies have shown that three lung cancer cell lines (H157, H611, and U2020) demonstrated selenium absorption and selenite cytotoxicity when treated with a 5 μM concentration for 5 hours. However, these cell lines were unaffected by selenate, even at concentrations exceeding 1 mM.[27] In contrast, Enqvist et al. (2011) found that selenate has beneficial effects on lung cancer patients. Specifically, selenate plays a critical role in natural killer (NK) cell-based anticancer immunotherapy by enhancing the susceptibility of cancer cells to attack by CD94/NK group 2A-positive NK cells. This highlights the potential of selenate in immunotherapy approaches, which aim to boost the immune system's ability to target and eliminate cancer cells.[28]

Some cancer cells, including HepG2, HeLa, and MCF-7 cells, can convert sodium selenite, a frequent dietary selenium metabolic step, to hydrogen selenide. According to Hu et al. (2018), this mechanism has the potential to cause cell death by accumulating in mitochondria, which can then impact the structure and function of mitochondria. The higher genotoxic stress caused by the inorganic selenium compounds may lead to decreased therapeutic efficacy, more systemic toxicity, and tumor burden.[29]

Separate selenium-containing substances

Through a variety of pathways, such as lowering oxidative stress, stimulating apoptotic processes, and increasing chemotherapeutic efficacy, these chemicals exert anticancer and chemo-preventive actions. Álvarez-Pérez et al. (2018) states that organic selenium compounds could be employed as anti-neoplastic drugs in the battle against solid tumors. Due to their anti-necrotic and pro-apoptotic properties, organic selenium compounds are preferred by many cancer patients. The reason behind this is that cancer cell necrosis, which is associated with the host inflammatory response, might lead to treatment-related problems.[30,31]

Essential natural compounds that include organoselenium

Minerals include selenium

Different cancer cells, including those from the lung, breast, colorectal, prostate, and melanoma tissues, were found to be extremely cytotoxic when exposed to selenium at concentrations varying from mild to high μmolar. Elements such as caspase activation, p53, endoplasmic reticulum stress, histone deacetylase inhibition, alterations in Bclxl, Bax, Bad, and Bim expression, decreases in cyclooxygenase-2 expression and glutathione peroxidase activity, and countless more were all involved in selenium-induced apoptosis.[32]

Selenochystine salt

Selenocystine, an amino acid byproduct formed when selenocysteine undergoes diselenide oxidation, plays a crucial role in inducing cytotoxic effects in various cancer types. Through disulfide reductases and low-molecular-weight thiols, highly reactive selenocysteine is effectively reduced from selenocystine. Studies have shown that selenocystine exhibits cytotoxicity in lung, breast, cervical, liver, and melanoma cancers, with cells in the low to medium micromolar range being particularly affected. The cytotoxicity of selenocystine leads to DNA damage and mitochondrial-mediated apoptosis, which is associated with p53 activation and an increase in reactive oxygen species (ROS) generation.[33]

Selenocystine not only induced cytotoxic effects but also activated the extrinsic/death receptor pathway in melanoma cells. In cervical cancer cells, selenocystine was shown to cause both apoptotic and paraptotic-like cell death. Wallenberg et al. (2014) further highlighted that this cell death is linked to endoplasmic reticulum (ER) stress, which triggers the unfolded protein response. In a mouse model of melanoma xenografts, selenocystine suppressed tumor growth without causing significant systemic damage.[34]

Additionally, a study by Fan et al. (2014) using a mouse lung cancer xenograft model found that both auranofin and selenocystine enhanced cell death. The remarkable efficacy of selenocystine against acute and chronic myeloid leukemia (AML) in humans was attributed largely to its action on immature leukocytes, rather than mature ones. Another beneficial side effect was its relative inertness to bone marrow, highlighting its potential as a therapeutic agent with fewer systemic side effects.[35]

Aspartate selenocysteine

Selenocysteine Se-conjugated β-lyases are responsible for converting mono-methylated selenoamino acids into methylselenol, an ester of the selenoamino acid. The production of the active metabolite, methylselenocysteine, varies across different cells, tissues, and organs. In vitro studies using various human cancer cells, including those from colon, breast, lung, and oral squamous cell lines, have shown that methylselenocysteine exhibits cytotoxic effects at micromolar concentrations. Methylselenocysteine therapy in vitro has been shown to reduce the expression of VEGF, though several questions remain about how it causes cell death. The role of the caspase-dependent pathway and the involvement of mitochondrial signaling in this process require further investigation.[36]

In addition to its cytotoxic properties, methylselenocysteine has demonstrated potential in enhancing chemotherapy effectiveness. It has been shown to improve the delivery of doxorubicin, increase microvessel density, vascular maturation, and function, and enhance blood vessel development, all while suppressing tumor growth in animal models. In breast cancer models, combining methylselenocysteine with tamoxifen has been found to synergistically inhibit tumor growth. Furthermore, when combined with irinotecan, methylselenocysteine has shown a synergistic effect in treating colon cancer and squamous cell carcinoma of the head and neck. This synergy was also observed in both drug-sensitive and drug-resistant cancer models, suggesting methylselenocysteine's potential as an effective adjuvant in cancer treatment.[37]

Vitamin Sulfurate

Melathione generates the metabolite selenodiglutathione when it reduces selenite. Glutathione then transforms selenodiglutathione into hydrogen selenide through the glutaredoxin and thioredoxin pathways. This pro-oxidant generates reactive oxygen species (ROS), such as superoxide and hydrogen peroxide, playing a key role in glutathione-dependent redox cycling. Exposure to low micromolar concentrations of selenodiglutathione has been shown to induce

apoptosis in various cancer cells, including those from the breast, ovarian, cervical, lymphoma, promyelocytic leukemia, and oral squamous cell lines. Recent studies have highlighted distinct differences between selenite and other cytotoxic agents, particularly in terms of their intracellular targets and expression patterns. These differences emphasize the unique role selenodiglutathione plays in cancer cell apoptosis and its potential as a therapeutic agent.[38,39]

Organic selenium components made

The chemistry of organoselenium compounds lagged behind that of organosulfur compounds until 1990, primarily due to the high degree of uncertainty and the potential toxicity of many selenium-containing compounds. However, recent discoveries highlighting selenium's crucial role in cancer, along with advancements in the synthesis and reactivity of organoselenium compounds, have led to the rapid development of new medical treatments. These developments have sparked renewed interest in organoselenium chemistry, particularly for its potential in cancer therapy and other medical applications.[40]

Antagonist for cholinesterase

Meliselenocysteine, the simplest organic selenium compound, undergoes oxidative decomposition to produce a chemical with notable medical applications. These compounds have been found to activate several caspase pathways, induce cytochrome c release, and trigger PARP cleavage, leading to cancer cell death across a variety of cell lines. Interestingly, while these compounds kill cancer cells, they do not rely on the presence of p53 as a determinant for cell death, even though they are effective only in cells with p53 (a key tumor suppressor gene). This makes them potentially useful for targeting a wide range of cancer cells that may harbor p53 mutations.[41]

Methylseleninic acid has demonstrated strong anticancer properties in multiple cancer models, including breast, lung, melanoma, and prostate cancers, in both in vivo and in vitro studies. Unlike normal peripheral blood mononuclear (PBM) cells, tumor-initiating polycytic leukemia (THP1) cells were found to be extensively damaged by methylseleninic acid. The anticancer effects of methylseleninic acid against malignant THP1 cells were shown to be dose-dependent, with significant effects observed at concentrations of 2.5, 5, and 15 μM over a 48-hour period. These findings underscore the potential of methylseleninic acid as an effective anticancer agent.[42]

Conclusion

Finally, selenocysteine, methylselenocysteine, and methylseleninic acid are only a few of the selenium compounds that have demonstrated promise as cancer treatments owing to their capacity to trigger cell death and influence important physiological functions. These chemicals have the potential to kill cancer cells by activating caspase pathways, which in turn release cytochrome c and cause DNA damage. Meliselenocysteine and other selenium-based chemicals do not depend on p53 to determine cell death, yet they are nevertheless effective against many different types of cancer cells. With dose-dependent cytotoxicity and normal cell sparing, methylseleninic acid in particular has shown encouraging anticancer effects across several cancer types. Their promise as cancer targeted therapeutics is expanding as more is learned about their action mechanisms and selenium compounds are synthesized better.

References

[1] Dong H, Li H, Fang L, Zhang A, Liu X, Xue F, Chen Y, Liu W, Chi Y, Wang W, Sun T, Ju M, Dai X, Yang R, Fu R, Zhang L. Increased reactive oxygen species lead to overactivation of platelets in essential thrombocythemia. Thromb Res. 2023 Jun;226:18-29. doi: 10.1016/j.thromres.2023.04.001. Epub 2023 Apr 10. PMID: 37087805.

[2] Maiorino M, Scapin M, Ursini F, Biasolo M, Bosello V, Flohé L. Distinct promoters determine alternative transcription of gpx-4 into phospholipid-hydroperoxide glutathione peroxidase variants. J Biol Chem. 2003;278:34286–34290. doi: 10.1074/jbc.M305327200.

[3] Vašková J, Kočan L, Vaško L, Perjési P. Glutathione-Related Enzymes and Proteins: A Review. Molecules. 2023 Feb 2;28(3):1447. doi: 10.3390/molecules28031447. PMID: 36771108; PMCID: PMC9919958.

[4] Chu Y, Lan RS, Huang R, Feng H, Kumar R, Dayal S, Chan KS, Dai DF. Glutathione peroxidase-1 overexpression reduces oxidative stress, and improves pathology and proteome remodeling in the kidneys of old mice. Aging Cell. 2020 Jun;19(6):e13154. doi: 10.1111/acel.13154. Epub 2020 May 13. PMID: 32400101; PMCID: PMC7294784.

[5] Barchielli G, Capperucci A, Tanini D. The Role of Selenium in Pathologies: An Updated Review. Antioxidants (Basel). 2022 Jan 27;11(2):251. doi: 10.3390/antiox11020251. PMID: 35204134; PMCID: PMC8868242.

[6] Hariharan S, Dharmaraj S. Selenium and selenoproteins: it's role in regulation of inflammation. Inflammopharmacology. 2020 Jun;28(3):667-695. doi: 10.1007/s10787-020-00690-x. Epub 2020 Mar 6. PMID: 32144521; PMCID: PMC7222958.

[7] Ridiandries A, Tan JTM, Bursill CA. The Role of Chemokines in Wound Healing. Int J Mol Sci. 2018 Oct 18;19(10):3217. doi: 10.3390/ijms19103217. PMID: 30340330; PMCID: PMC6214117.

[8] Guo, Q., Jin, Y., Chen, X. et al. NF-κB in biology and targeted therapy: new insights and translational implications. Sig Transduct Target Ther 9, 53 (2024). https://doi.org/10.1038/s41392-024-01757-9

[9] Seiderer J, Dambacher J, Kühnlein B, Pfennig S, Konrad A, Török HP, Haller D, Göke B, Ochsenkühn T, Lohse P, Brand S. The role of the selenoprotein S (SELS) gene -105G>A promoter polymorphism in inflammatory bowel disease and regulation of SELS gene expression in intestinal inflammation. Tissue Antigens. 2007 Sep;70(3):238-46. doi: 10.1111/j.1399-0039.2007.00888.x. PMID: 17661913.

[10] Liu Z. Antioxidant activity of the thioredoxin system. Biophys Rep. 2023 Feb 28;9(1):26-32. doi: 10.52601/bpr.2023.230002. PMID: 37426202; PMCID: PMC10323771.

[11] Seiderer J, Dambacher J, Kühnlein B, Pfennig S, Konrad A, Török HP, Haller D, Göke B, Ochsenkühn T, Lohse P, Brand S. The role of the selenoprotein S (SELS) gene -105G>A

promoter polymorphism in inflammatory bowel disease and regulation of SELS gene expression in intestinal inflammation. Tissue Antigens. 2007 Sep;70(3):238-46. doi: 10.1111/j.1399-0039.2007.00888.x. PMID: 17661913.

[12] Burk RF, Hill KE. Selenoprotein P-expression, functions, and roles in mammals. Biochim Biophys Acta. 2009 Nov;1790(11):1441-7. doi: 10.1016/j.bbagen.2009.03.026. Epub 2009 Apr 1. PMID: 19345254; PMCID: PMC2763998.

[13] Lau ATY, Tan HW, Xu YM. Epigenetic effects of dietary trace elements. Curr Pharmacol Rep. 2017;3:232–241. doi: 10.1007/s40495-017-0098-x.

[14] Vinceti M, Filippini T, Cilloni S, Bargellini A, Vergoni AV, Tsatsakis A, Ferrante M. Health risk assessment of environmental selenium: emerging evidence and challenges. Mol Med Rep. 2017;15:3323–3335. doi: 10.3892/mmr.2017.6377.

[15] Vinceti M, Wei ET, Malagoli C, Bergomi M, Vivoli G. Adverse health effects of selenium in humans. Rev Environ Health. 2001;16:233–251. doi: 10.1515/REVEH.2001.16.4.233.

[16] Rahmanto AS, Davies MJ. Selenium-containing amino acids as direct and indirect antioxidants. IUBMB Life. 2012;64:863–871. doi: 10.1002/iub.1084

[17] Prasad S, Gupta SC, Tyagi AK. Reactive oxygen species (ROS) and cancer: role of antioxidative nutraceuticals. Cancer Lett. 2017;387:95–105. doi: 10.1016/j.canlet.2016.03.042

[18] Georgieva E, Ivanova D, Zhelev Z, Bakalova R, Gulubova M, Aoki I. Mitochondrial dysfunction and redox imbalance as a diagnostic marker of “free radical diseases” Anticancer Res. 2017;37:5373–5381.

[19] Brigelius-Flohé R, Flohé L. Selenium and redox signaling. Arch Biochem Biophys. 2017;617:48–59. doi: 10.1016/j.abb.2016.08.003.

[20] Fernandes AP, Gandin V. Selenium compounds as therapeutic agents in cancer. Biochim Biophys Acta. 2015;1850:1642–1660. doi: 10.1016/j.bbagen.2014.10.008.

[21] Misra S, Boylan M, Selvam A, Spallholz JE, Bjornstedt M. Redox-active selenium compounds—from toxicity and cell death to cancer treatment. Nutrients. 2015;7:3536–3556. doi: 10.3390/nu7053536

[22] Choi A, Jo MJ, Jung MJ, Kim HS, Yoon S. Selenate specifically sensitizes drug-resistant cancer cells by increasing apoptosis via G2 phase cell cycle arrest without P-GP inhibition. Eur J Pharmacol. 2015;764:63–69. doi: 10.1016/j.ejphar.2015.06.046.

[23] Kieliszek M, Lipinski B, Blazejak S. Application of sodium selenite in the prevention and treatment of cancers. Cells. 2017;6:39. doi: 10.3390/cells6040039.

[24] Tan HW, Xu YM, Wu DD, Lau ATY. Recent insights into human bronchial proteomics—how are we progressing and what is next? Expert Rev Proteom. 2018;15:113–130. doi: 10.1080/14789450.2017.1417847

[25] Berthier S, Arnaud J, Champelovier P, Col E, Garrel C, Cottet C, Boutonnat J, Laporte F, Faure P, Hazane-Puch F. Anticancer properties of sodium selenite in human glioblastoma cell cluster spheroids. J Trace Elem Med Biol. 2017;44:161–176. doi: 10.1016/j.jtemb.2017.04.012.

[26] Lipinski B. Sodium selenite as an anticancer agent. Anticancer Agents Med Chem. 2017;17:658–661. doi: 10.2174/1871520616666160607011024

[27] Olm E, Fernandes AP, Hebert C, Rundlöf AK, Larsen EH, Danielsson O, Björnstedt M. Extracellular thiol-assisted selenium uptake dependent on the xc-cystine transporter explains the cancer-specific cytotoxicity of selenite. PNAS. 2009;106:11400–11405. doi: 10.1073/pnas.0902204106.

[28] Enqvist M, Nilsonne G, Hammarfjord O, Wallin RPA, Bjorkstrom NK, Bjornstedt M, Hjerpe A, Ljunggren HG, Dobra K, Malmberg KJ, Carlsten M. Selenite induces posttranscriptional blockade of HLA-E expression and sensitizes tumor cells to CD94/NKG2A-Positive NK Cells. J Immunol. 2011;187:3546–3554. doi: 10.4049/jimmunol.1100610.

[29] Hu B, Cheng R, Gao X, Pan X, Kong F, Liu X, Xu K, Tang B. Targetable mesoporous Silica nanoprobes for mapping the subcellular distribution of H2Se in cancer cells. ACS Appl Mater Interfaces. 2018;10:17345–17351. doi: 10.1021/acsami.8b02206.

[30] Álvarez-Pérez M, Ali W, Marc MA, Handzlik J, Domínguez-Álvarez E. Selenides and diselenides: a review of their anticancer and chemopreventive activity. Molecules. 2018;23:628. doi: 10.3390/molecules23030628.

[31] Ali W, Álvarez-Pérez M, Marc MA, Salardón-Jiménez N, Handzlik J, Domínguez-Álvarez E. The anticancer and chemopreventive activity of selenocyanate-containing compounds. Curr Pharmacol Rep. 2018;4:468–481. doi: 10.1007/s40495-018-0160-3.

[32] Yang Y, Huang F, Ren Y, Xing L, Wu Y, Li Z, Pan H, Xu C. The anticancer effects of sodium selenite and selenomethionine on human colorectal carcinoma cell lines in nude mice. Oncol Res. 2009;18:1–8. doi: 10.3727/096504009789745647.

[33] Hariharan, S., Dharmaraj, S. Selenium and selenoproteins: it's role in regulation of inflammation. Inflammopharmacol 28, 667–695 (2020). https://doi.org/10.1007/s10787-020-00690-x

[34] Wallenberg M, Misra S, Wasik AM, Marzano C, Björnstedt M, Gandin V, Fernandes AP. Selenium induces a multi-targeted cell death process in addition to ROS formation. J Cell Mol Med. 2014;18:671–684. doi: 10.1111/jcmm.12214.

[35] Fan C, Zheng W, Fu X, Li X, Wong YS, Chen T. Enhancement of auranofin induced lung cancer cell apoptosis by selenocystine, a natural inhibitor of TrxR1 in vitro and in vivo. Cell Death Dis. 2014;5:e1191. doi: 10.1038/cddis.2014.132

[36] Seale, L. A. (2019). Selenocysteine β-Lyase: Biochemistry, Regulation and Physiological Role of the Selenocysteine Decomposition Enzyme. Antioxidants, 8(9), 357. https://doi.org/10.3390/antiox8090357

[37] Valentina Gandin, Prajakta Khalkar, Jeremy Braude, Aristi P. Fernandes, Organic selenium compounds as potential chemotherapeutic agents for improved cancer treatment, Free Radical Biology and Medicine, Volume 127, 2018, Pages 80-97, ISSN 0891-5849, https://doi.org/10.1016/j.freeradbiomed.2018.05.001.

[38] Tobe T, Ueda K, Ando M, Okamoto Y, Kojima N. Thiol-mediated multiple mechanisms centered on selenodiglutathione determine selenium cytotoxicity against MCF-7 cancer cells. J Biol Inorg Chem. 2015;20:687–694. doi: 10.1007/s00775-015-1254-6.

[39] Wallenberg M, Misra S, Wasik AM, Marzano C, Björnstedt M, Gandin V, Fernandes AP. Selenium induces a multi-targeted cell death process in addition to ROS formation. J Cell Mol Med. 2014;18:671–684. doi: 10.1111/jcmm.12214.

[40] Nogueira CW, Barbosa NV, Rocha JBT. Toxicology and pharmacology of synthetic organoselenium compounds: an update. Arch Toxicol. 2021 Apr;95(4):1179-1226. doi: 10.1007/s00204-021-03003-5. Epub 2021 Apr 1. PMID: 33792762; PMCID: PMC8012418.

[41] Radomska D, Czarnomysy R, Radomski D, Bielawski K. Selenium Compounds as Novel Potential Anticancer Agents. Int J Mol Sci. 2021 Jan 20;22(3):1009. doi: 10.3390/ijms22031009. PMID: 33498364; PMCID: PMC7864035.

[42] Hu, Wenli & Ma, Yurong & Zhao, Chong & Yin, Shutao & Hu, Hongbo. (2021). Methylseleninic acid overcomes programmed death-ligand 1-mediated resistance of prostate cancer and lung cancer. Molecular Carcinogenesis. 60. 10.1002/mc.23340.