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Targeting selenium metabolism and selenoproteins: Novel avenues for drug discovery

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Abstract

Selenoproteins play a wide range of roles in metabolism and oxidative stress defense and are produced by organisms in all three domains of life. Recent evidence has been presented that metal based cancer drugs target the selenol nucleophile of the active site selenocysteine in thioredoxin reductase isoenzymes. Other metals and metalloids, such as tin, arsenic and gold, have also recently been shown to form stable complexes with hydrogen selenide, a required precursor for the synthesis of selenoproteins in all biological organisms. Moreover these metal based compounds have been shown to inhibit growth of pathogens such as *Clostridium difficile* and *Treponema denticola* due to their reactivity with this highly reactive metabolic precursor. This review summarizes the recent finding on these two avenues for drug discovery, and puts this work in context with the larger field of selenium biology.

Introduction

Our understanding of the role of selenium in biology is constantly evolving. Initially known as an environmental toxin, it was first recognized as an essential trace element for several organisms in the 1950s.[1–3] Selenoproteins, in which selenium is incorporated as the unique amino acid seleno-cysteine, were discovered in 1973.[4,5] Since that time seleno-proteins have been identified across all three domains of life and there are at least twenty-five human selenoproteins.[6,7] Selenium deficiency is associated with a wide variety of human diseases including cancer, cardiovascular disease, male infertility, and immune suppression and selenoproteins are critical players in a variety of essential biological processes.[8,9]

Selenoprotein synthesis is complex, consisting of many steps and involving a cadre of specialized protein machinery. Briefly, the process requires the production of seleno-phosphate from the highly reactive, reduced form of selenium, hydrogen selenide. This is performed in an ATP dependent manner by the enzyme selenophosphate synthetase.[10–14] It should be noted that little is understood regarding the transport and reduction of selenium upstream of this enzyme. Selenocysteine is then synthesized by reaction of seleno-phosphate with a serine charged *t*RNA.[15,16] This serine must be first phosphorylated in archeabacteria and eukaryotes by a recently identified kinase.[17,18] Insertion of selenocysteine into the polypeptide chain is uniquely encoded by the stop codon, UGA.[19] Specialized translation factors interact with a stem-loop structure in the mRNA to recruit the selenocysteine bound *t*RNA to the ribosome. This structure is known as the selenocysteine insertion sequence (SECIS) element and is located immediately downstream of the UGA codon in the coding region in prokaryotes and within the 3′ untranslated region in archeabacteria and eukaryotes.[20–23]

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The importance of selenoproteins to human health is not fully understood. Much research has been devoted to the positive role of selenium and selenoproteins with regards to their critical role in defense against oxidative stress. This has been coupled in recent years with an emphasis on the benefits of nutritional supplementation, from cell culture model systems to animal studies and even human clinical trials. Recent studies, however, have demonstrated that supplementation with selenium may somehow contribute to diabetes, thus complicating future studies that attempt to link selenium nutritional status with human health.[24–26] In this review we examine the role of selenoproteins in the supporting human disease and demonstrate that their unique biosynthetic process and highly specialized functions make them ideal targets for drug discovery.

Selenoproteins and cancer

The role of selenoproteins in cancer prevention has been the subject of much study and debate. Epidemiological studies have linked polymorphisms in selenoproteins with increased cancer risk.24,27 Two such selenoproteins, with selenocysteine at their active sites, glutathione peroxidase (Gpx) and thioredoxin reductase (TrxR), are involved in defense and repair of oxidative damage. Gpx catalyzes the reduction of hydroperoxides and lipid peroxides to their corresponding alcohols and water using glutathione as the electron donor.28,29 TrxR catalyzes the NADPH dependent reduction of thioredoxin (Trx) and other oxidized dithiols.30 Given the integral role of oxidative stress in carcinogenesis, it has been hypothesized that ensuring adequate expression and optimal activity of these enzymes is an important aspect of cancer prevention.31 In addition, low molecular weight selenium compounds have been identified with direct anticancer properties.32

Much of current research regarding selenium and cancer has focused on the chemopreventative effect of nutritional selenium supplementation.[33,34] This has been the subject of several clinical trials. Early data from the Nutritional Prevention of Cancer trial in 1996 demonstrated a significant decrease in overall cancer incidence and mortality in the selenium treatment group.[31] More recently, however, the complete results of the SELECT trial have cast doubt on the efficacy of dietary selenium supplementation.[25,35,36] These conflicting results reflect the complexity of the role of selenium in human health and underscore the need for further research to understand selenium biology at the molecular level before embarking on additional large scale clinical studies.

Although there is a large body of research supporting the role of selenium in cancer prevention, there is also research indicating that selenium and selenoproteins play a role in cancer promotion. Acute selenium toxicity can result in hair loss, damage to skin and nails, unsteady gait and paralysis.[37] This toxicity is attributed to the generation of reactive oxygen species during the metabolic processing of selenium compounds and, as such, high doses of selenium are considered carcinogenic.[38] Recent attention, however, has turned to the importance of selenoproteins in supporting carcinogenesis. Several studies indicate that the production of certain seleno-proteins is upregulated in cancer cells and tumors.[39–44] In particular, a link between increased levels of TrxR1 and tumor formation has been well established.[45,46] On the other hand, selenoprotein deficiency has been shown to suppress cancer development in a mouse liver cancer model.[47] Given these contrasting views, selenoproteins playing a role both in prevention of carcinogenesis and a role in increased metabolic potential in tumors, we will discuss further the literature surrounding the inhibition of selenoenzymes as a viable target for novel chemotherapy approaches.

Inhibition of thioredoxin reductase (TrxR)

TrxR is the focus of much of the current research on development of novel therapies for cancer treatment.48,49 Both a cytosolic (TrxR1) and a mitochondrial enzyme (TrxR2) are

present in essentially all cell types and tissues. These enzymes are important regulators of redox balance and together these isoenzymes participate in a wide variety of activities including cell proliferation, transcription, DNA repair, angiogenesis, cell signaling, and embryogenesis.[42,50–52] TrxR1 has a broad substrate specificity, but is the only enzyme to reduce thioredoxin (Trx), converting the reducing potential from NADPH to drive metabolic processes throughout the cell.[49] The C-terminal sequence -Gly-Cys-SeCys-Gly is required for this enzyme activity.[53] The relationship of TrxR to cell cycle control is multifaceted. It is known to directly activate the p53 tumor suppressor and, through reduction of Trx, is intimately tied to the regulation of apoptosis.[49,54]

Although primarily considered to play a central role maintaining Trx pools for many 'antioxidant' enzymes (peroxiredoxins, methionine sulfoxide reductases) in cancer prevention, it is becoming increasingly clear that TrxR is also critical for cancer cell proliferation. Several cancer cell lines and tumors exhibit increased production of TrxR.[39,40,42–44] In addition, upregulation of Trx is associated with resistance to chemotherapy.[55,56] Knock down of TrxR has been shown to inhibit DNA replication and growth in cancer cells and reverse tumor phenotype.[46,57] These studies suggest that TrxR can be a good target for development of agents that reduce tumor growth, perhaps in combination with existing drugs that selectively kill aggressive tumors.

The C-terminal location of the highly reactive selenocysteine residue in TrxR makes it susceptible to inhibition by electrophilic compounds.[58] Several compounds have been shown to inhibit TrxR. These include drugs that are currently used in chemotherapy and others with potential for therapeutic development. Cisplatin, a platinum containing drug widely used in cancer chemotherapy, irreversibly inhibits TrxR.[59] Gold compounds have long been studied for their anticancer activity.[60] Auranofin [2,3,4,6-tetra-*o*-acetyl-1-thio-*β*-D-gluco-pyranosato-*S*-(triethyl-phosphine) gold], used to treat Rheumatoid arthritis, inhibits selenoenzymes through interactions with the reduced selenocysteine residues at the active sites. It strongly inhibits TrxR at low nanomolar concentrations *in vitro*.[61] In addition, auranofin was recently shown to induce apoptosis in a cisplatin resistant ovarian cancer cell line by altering the redox state of the cells.[62] Several other gold compounds have also been shown to inhibit TrxR and the anticancer potential of such compounds continues to be the subject of much research.[63–65] Recently the mechanism of arsenic trioxide (ATO), used in the treatment of acute promyelocytic leukemia was attributed to TrxR inhibition *in vitro*.[66] In addition, motexafin gadolinium, mansonone F and even curcumin have demonstrated anticancer activity through inhibition of TrxR.[67–69] Many of these drugs are showing promising results in early stage clinical trials.[70]

The effects of TrxR inhibition are two-fold. The first is a reduction in the available pool of reduced Trx, leading to a decrease in the activity of many antioxidant enzyme systems that require Trx as an electron donor. This will result in an accumulation of reactive oxygen species and alteration of the redox state within the cell. Trx is directly involved in regulation of apoptosis through interactions with ASK1, procaspase 3 and NF-κB and thus TrxR inhibition promotes apoptosis.[49] In addition, inhibition of TrxR can result in formation of SecTRAPs (selenium compromised thioredoxin reductase-derived apoptotic proteins), in which the active site selenocysteine residue has been rendered inactive by electrophilic compounds. These SecTRAPS maintain NADPH oxidase activity, leading to increases in the level of superoxide and subsequently downstream reactive oxygen and nitrogen species (hydrogen peroxide and peroxynitrite). They have been associated with increased intracellular oxidative stress and cell death *via* both apoptosis and necrosis.[71,72]

Inhibition of selenoprotein synthesis

While specifically targeting selenoproteins, we must also account for the possibility of inhibiting selenoprotein synthesis as a whole. This has profound implications in terms of understanding the mechanism of these drugs *in vivo* and also with regard to the impact of concurrent selenium supplementation. Given that many TrxR inhibitors exhibit reactivity with active site selenols, the possibility exists that they could interact with reactive selenium metabolites upstream of selenophosphate synthetase, such as HSe^-, thus blocking selenoprotein synthesis entirely. There is precedent since it has been shown that arsenic compounds can form stable conjugates with hydrogen selenide, leading to a reduction in the bioavailable pool of selenium for selenoproteins synthesis.[73–77] Arsenite, auranofin and ATO have all been shown to inhibit selenoprotein synthesis in cell culture.[77] The inability to make new selenoproteins combined with direct enzyme inhibition may produce a synergistic effect, improving the efficacy of drugs to reduce proliferation of cells and induce apoptosis due to a reduced capacity to produce all selenoproteins. These questions will likely be the focus of future studies that address the mechanism of action of drugs like auranofin in the treatment of cancer.

Selenoproteins and infectious disease

Few studies have examined the role of selenoproteins in human pathogens. Many important human pathogens, both prokaryotic and eukaryotic, rely upon selenoproteins for their survival. The unique reactivity of selenocysteine and the specialized machinery required for selenoprotein synthesis make selenoproteins attractive targets for antimicrobial development. It should be noted that, based on computational analysis of genomes, only 14% of eubacteria encode seleno-proteins,[6] suggesting agents that block selenoproteins would be ‘narrow-spectrum’ agents.

Bacteria

Computational analysis of completed genome sequences has identified selenoproteins in several bacterial pathogens including Campylobacter jejeuni, Escherichia coli, Haemophilus influenza, and *Salmonella typhimurium*.[78] *Clostridium difficile*, the primary causative agent of antibiotic associated diarrhea, relies upon two selenoenzymes, glycine reductase and D-proline reductase, for energy metabolism *via* Stickland fermentation of amino acids.[79] Similarly, *Treponema denticola*, implicated in periodontal disease, participates in Stickland reactions and exhibits a strict nutritional requirement for selenium.[80]

Recent work has examined the impact of auranofin, on the growth of *C. difficile*.[81] Auranofin potently inhibits the growth of *C. difficile* but does not similarly affect other clostridia that do not utilize selenoproteins to obtain energy. Although it is a known selenoenzyme inhibitor, it was shown that auranofin inhibited the new synthesis of selenoproteins using a sensitive radioisotope labeling approach. Specifically, the drug was found to react directly with HSe^-, which is required for selenoprotein synthesis, to form a stable complex. This complex was identified using mass spectrometry and confirmed using X-ray absorption spectroscopy. Auranofin blocks the uptake of selenium and results in the accumulation of the auranofin-selenide adduct in the culture medium. The resulting deficiency in selenium available for selenoprotein synthesis, *i.e.* bioavailable selenium, inhibited growth of *C. difficile*.

T. denticola is similarly affected by auranofin.[82] Interestingly, stannous salts, which are commonly used in toothpastes and other oral treatments, also block selenium metabolism in this organism. These studies demonstrate that targeting nutritional selenium availability, rather than specific enzyme inhibition may provides a new avenue for antimicrobial development against selenium-dependent pathogens.

Parasites

Tropical diseases are frequently neglected in therapeutic development research, but yet are responsible for a huge burden of disease worldwide. The impact of malaria is well known with approximately 500 million *Plasmodium falciparum* infections annually.[83] In addition, an estimated 166 million people are infected with schistosomes in sub-Saharan Africa alone with approximately 280 000 deaths per year.[84] There is an endless selection of eukaryotic parasites that impact human health throughout the world. The number of available treatments, however, for diseases caused by these organisms is extremely limited.

Recently selenoproteins have been identified in a number of parasitic organisms including trypanosomes and platyhelminths.[85,86] In addition, selenoproteins in *Plasmodium falciparum* have been suggested as possible targets for therapeutic development.[87] So far, the strategy of targeting selenoproteins is most developed in the battle against schistosomiasis. The primary treatment for this disease is broad distribution of praziquantel, but the possibility of the development of drug resistance and the lack of adequate alternatives has emphasized the need for new drug development.[88]

Unlike mammalian cells that rely upon two separate enzymes, glutathione reductase and thioredoxin reductase, to maintain the level of reduced thiols, schistosomes utilize a hybrid of the two systems known as thioredoxin glutathione reductase (TGR).[89] It is a unique selenoenzyme that is essential for growth of the organism. Similar to human thioredoxin reductase, TGR possesses a C-terminal seleno-cysteine residue that is required for activity and is inhibited by auranofin.90 These properties of TGR make it an attractive target for further study. High throughput screening has yielded a number of compounds with inhibitory action against TGR.91 Further study of these compounds has identified oxadiazole 2-oxides as new lead compounds for treatment of schistosomiasis.92 These positive results provide further evidence that specifically targeting selenoproteins is a viable avenue in the search for new drugs against schistosomes and other organisms that rely upon selenoproteins for growth.

Final discussion

It is clear that selenoproteins in mammals can function both in central metabolism and DNA synthesis, while also playing a role in defense against reactive oxygen species. In microbial pathogens, selenoproteins can play a critical role in energy metabolism and potentially other aspects of cellular physiology as well. Recent discoveries in bioinorganic chemistry and selenoprotein enzymology suggest that targeting of specific selenoproteins, or the metabolism of selenium, can be a rich avenue for drug discovery. Current and future studies will likely uncover more ways to target selenium and seleno-proteins for improvements in human health.

Biography

Sarah Elizabeth Jackson-Rosario

Sarah Jackson-Rosario is a post-doctoral fellow in the School of Medicine at Mercer University in Macon, Georgia. She received a Master's degree in Public Health in Tropical and Communicable Diseases from the University of South Florida in 2002. In 2009, she received her PhD from the University of Central Florida while working on selenium metabolism and pathogenesis of Clostridium difficile in the laboratory of William Self.

William Thomas Self

William Self is an Associate Professor in the Burnett School of Biomedical Science at the University Of Central Florida College Of Medicine. He began studying metallo-enzymes during his doctoral research at the University of Florida, studying transcriptional regulation of genes encoding molybdoenyzmes. His interest in selenium metabolism and selenoproteins began during his time as a Research Fellow NIH in Bethesda, Maryland under the guidance of Thressa Stadtman. His research is now focused on understanding the metabolic pathways used for selenium transport, reduction and incorporation into selected seleno-proteins in bacteria and mammals, as well as studying the role of poorly understood selenoproteins in model systems.

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