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FORUM EDITORIAL

Selenium and Selenoproteins in Health and Disease

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Abstract

The beneficial role of the trace element selenium (Se) in human health has been known for several decades and is attributed both to low-molecular-weight Se compounds and to its presence within 25 selenoproteins in the form of the amino acid selenocysteine (Sec). Incorporation of Sec into selenoproteins involves decoding of the UGA codon. This process requires multiple features, such as the Sec-insertion sequence (SECIS) element and protein factors, including a specific elongation factor EFSec and the SECIS-binding protein 2, SBP2. Although many selenoproteins remain functionally uncharacterized, some of their known functions include redox regulation of intracellular signaling, redox homeostasis, and thyroid hormone metabolism. Pathologically, reduced expression of selenoproteins has been directly linked with the congenital muscle disease referred to as selenoprotein N (SEPN)-related myopathy and with thyroid-hormone metabolism defects (deficiency of deiodinases due to genetic defects in SBP2). From a broader, less well defined aspect, selenium compounds and selenoproteins have been linked to prevention of some forms of cancer, Alzheimer's disease, cardiovascular disease, and life span. This forum summarizes recent advances in our understanding of important roles of selenium, selenoproteins, and factors involved in selenoprotein synthesis in health and disease and discusses potential targets for therapy. *Antioxid. Redox Signal.* 12, 793–795.

Selenium (Se) compounds like selenite, selenate, or selenomethionine have a history of proving that Se, an essential trace element with a solid reputation for being good for human and animal health, has antioxidant and cancer-preventive effects (10). The incorporation of selenium as selenocysteine (Sec) in 25 proteins by a highly elaborate cotranslational mechanism has defined the human selenoproteome (6), in which the precise function of about half of the proteins is still unknown. Many of the characterized proteins have functions ranging from antioxidants or oxidoreductases, including glutathione peroxidases (GPxs) and thioredoxin reductases (TrxR), metabolism of thyroid hormones (deiodinases; DIOs), transport and delivery of selenium to peripheral tissues (selenoprotein P; SelP), protein folding, and endoplasmic reticulum (ER) stress (Sep15, SelM, Sel N, and Sel S) (10). Sec incorporation at UGA codons in selenoproteins requires unique features, such as the SECIS element located in the 3′-UTR of eukaryotic selenoprotein mRNAs, and is mediated by a multiprotein complex that includes Sec-insertion sequence (SECIS)–binding protein 2 (SBP2), the Sec-specific elongation factor (EFSec), and the ribosomal protein L30.

Several articles in this forum summarize the advances in our understanding of functions of characterized selenoproteins. The first four articles in the series present original research data. Papp *et al.* (9) investigate the effect of antisense oligonucleotide (ASO)-mediated SBP2 depletion in cell-culture models. Contrary to previous studies, which could obtain only partial SBP2 depletion, an almost complete depletion of SBP2 was achieved by using ASOs, which had a dramatic effect on cell viability. SBP2-depleted cells showed a large increase in reactive oxygen species (ROS), leading to DNA damage, stress granule formation, and lipid peroxidation. The massive cellular damage appears to overwhelm the repair capacity and rapidly activates cytochrome *c*– and caspase-dependent apoptosis. This was not unexpected, because selenoproteins are dramatically reduced because of the lack of SBP2, and interestingly, small-molecule antioxidants such as *N*-acetylcysteine, α-tocopherol, and glutathione administered to cell cultures individually or combined were unable to rescue completely the apoptotic phenotype. Importantly, because animal models of SBP2 gene deletion have not yet been reported, this study establishes that SBP2 is essential for cell survival. Future studies using the conditional knockout mouse model of the SBP2 gene will yield important insights into the loss of SBP2 in tissue malfunction and disease development. In line with the role of selenoproteins in protection against ROS-induced cellular damage and cell death is the article by Reeves *et al.* (11), which indicates that overexpression of selenoprotein

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M in neuronal cells protects against hydrogen peroxide–induced oxidative stress, and conversely, its depletion leads to an increase in ROS and the decreased viability of neurons. The study also provides evidence that Sel M influences the process through which cells release calcium from internal stores, highlighting the potential importance of Sel M in calcium regulation for neuronal viability and responses to oxidative stress.

In the brain, lipid peroxidation is the predominant consequence of oxidative stress, and increased lipid peroxidation is known to be an early event in the etiology of Alzheimer's disease (15). Glutathione peroxidase 4 (GPx4) is an essential antioxidant selenoenzyme well known to protect against lipid peroxidation. In the next study, Yoo *et al*. (16) show that GPx4 protein, but not mRNA, was downregulated in brain tissues of Alzheimer-diseased mice that correlated with elevated levels of oxidized lipid by-products malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE). Moreover, increased levels of 4-HNE were also found in Alzheimer-diseased human brain. Interestingly, the downregulation of GPx4 was found to correlate with decreased levels of the translation factor GRSF1, which specifically controls translation of GPx4. Overall, this study suggests an important role of GPx4 in protecting the brain from oxidative insult by preventing against lipid hydroperoxide accumulation.

Another type of cellular damage implicated in neurodegeneration and aging is oxidized methionine residues. Oxidation of methionine residues is a common event, induced by intracellular redox signaling or ROS, and consists of a mixture of *S*- and *R*-epimers of methionine sulfoxide. The selenoenzyme methionine sulfoxide reductase B1 (MsrB1) selectively reduces the methinonine *S*-sulfoxide back to methionine, and thus plays an important protein-repair function in the cell. MsrB1 is also one of the selenoproteins regulated by the selenium status in the diet, with selenium deficiency reducing its expression in mice (7). The article by Novoselov *et al*. (8) used several mouse models to study MsrB1 regulation with dietary selenium status, calorie restriction, and aging. Importantly, the study found that MsrB1 is the major Msr in mouse liver, and its expression and activity are highly regulated by dietary selenium. Selenium deficiency dramatically reduced MsrB1 levels under normal and calorie-restricted diets, and MsrB1 activity decreased with aging, independent of the selenium status in the diet. MsrB1 appears to be one of the most susceptible proteins to minor dietary changes in the amount of selenium and could thus be used as a highly useful marker of selenium status in humans. Although MsrB1 does not seem to be the basis of calorie restriction–dependent increase in life span, selenium, by influencing the activity of MsrB1, and MsrB1, by preventing accumulation of oxidized methionine residues and calorie restriction, may act synergistically in the extension of life span.

The second part of this forum comprises six review articles. Schendrina *et al*. (14) discuss the structure–function relation and evolutionary trends of the seven mammalian selenoproteins that reside within the ER. The ER compartment is known for its redox processes, such as disulfide bond formation, and this review highlights the recently identified unique linkages between individual selenoproteins and the redox processes in the ER. Conrad and Schweizer (1) discuss in their review the subject of targeted gene deletion of individual selenoproteins in mice, which has proven instrumental in providing the basis for elucidation of biologic function and possible roles of selenoproteins in disease prevention. In the article by Selenius *et al*. (13), selenium and the selenoprotein thioredoxin reductase are discussed in the prevention, treatment, and diagnosis of cancer. This coupling between selenoproteins and cancer has a background, in that several clinically used cancer drugs are targeting thioredoxin reductase and its essential selenothiol. Thioredoxin reductase is involved in thioredoxin-dependent ribonucleotide reduction as well as antioxidant and antiapoptotic effects. This article discusses recent advances in cancer-preventive effects of selenium compounds and also how higher concentrations of an agent like selenite or monomethylselenol can be used to target selectively the growth of cancer cells.

The molecular mechanism that governs the co-translational incorporation of selenocysteine (Sec) during selenoprotein synthesis in eukaryotic systems is less well understood compared with that in prokaryotes; nevertheless, great advances have been made in discovering several factors involved in this intricate process in recent years. In their review, Donovan and Copeland (3) provide a comprehensive overview of the factors involved in the eukaryotic Sec-incorporation process and discuss the current understanding of the chain of events that leads to incorporation of Sec into selenoproteins.

Despite the identification and characterization of several proteins involved in selenoprotein synthesis, none of these Sec incorporation factors, except $tRNA^{Sec}$, has been targeted in animal models. Until recently, genetic mutations in humans with a clinical phenotype directly related to Sec-incorporation defects were reported only for the *SEPN1* gene, the absence of which is known to cause a genetic disease referred to as SEPN1-related myopathy (SEPN1-RM1). It includes disorders ranging from the classic form of multiminicore disease, congenital muscular dystrophy with spinal rigidity and restrictive respiratory syndrome, and desmin-related myopathy with Mallory body–like inclusions. The review by Arbogast and Ferreiro (12) provides a comprehensive characterization of SEPN1-RM1 genetic defects, a general overview of the role and functions of Sel N as a regulator of redox signaling, cell stress, and calcium homeostasis; the link between Sel N and ryanodine receptor; discussion of cellular and animal models that elucidate pathophysiologic mechanisms underlying SEPN1-RM1; and how the knowledge gained has been mined for the new treatment modalities for this genetic disease.

More recently, mutations in *SECISBP2*/*SBP2* gene, a key factor for the co-translational insertion of Sec into selenoproteins, have been described in humans. Dumitrescu *et al*. (5) were the first group to describe two families with mutations in the *SBP2* gene that had abnormal thyroid-function tests and growth retardation. Subsequently, another family manifested a similar clinical phenotype and was found to harbor a different *SBP2* mutation (2). In their review, Dumitrescu *et al*. (4) describe the different SBP2 mutations identified so far and provide a detailed discussion of the clinical presentation and clinical course of subjects with SBP2 mutations. Moreover, new insights into the effects of *SBP2* mutations on protein function and expression of selenoproteins that have emerged from *in vitro* studies, as well as the results from *in vivo* studies on monitoring the effects of selenium and thyroid-hormone supplementation in subjects with *SBP2* mutations are discussed.

We hope this forum issue will provide the reader with a framework to understand current concepts in selenium and

the selenoprotein field, their critical role in the maintenance of antioxidant defence, cancer prevention, and their effects on longevity and thyroid-hormone metabolism. We thank all the authors who made this forum possible. Their timely contributions bring us up to date on this crucial area of research on the close link between selenium and selenoproteins.

References

1. Conrad M and Schweizer U. Unveiling the molecular mechanisms behind selenium-related diseases through knockout mouse studies. *Antioxid Redox Signal* 12: 851–865, 2010.
2. Di Cosmo C, McLellan N, Liao XH, Khanna KK, Weiss RE, Papp L, and Refetoff S. Clinical and molecular characterization of a novel selenocysteine insertion sequence-binding protein 2 (SBP2) gene mutation (R128X). *J Clin Endocrinol Metab* 94: 4003–4009, 2009.
3. Donovan J and Copeland PR. Threading the needle: getting selenocysteine into proteins. *Antioxid Redox Signal* 12: 881–892, 2010.
4. Dumitrescu AM, Di Cosmo C, Liao XH, Weiss RE, and Refetoff S. The syndrome of inherited partial SBP2 deficiency in humans. *Antioxid Redox Signal* 12: 905–920, 2010.
5. Dumitrescu AM, Liao XH, Abdullah MS, Lado-Abeal J, Majed FA, Moeller LC, Boran G, Schomburg L, Weiss RE, and Refetoff S. Mutations in SECISBP2 result in abnormal thyroid hormone metabolism. *Nat Genet* 37: 1247–1252, 2005.
6. Kryukov GV, Castellano S, Novoselov SV, Lobanov AV, Zehtab O, Guigo R, and Gladyshev VN. Characterization of mammalian selenoproteomes. *Science* 300: 1439–1443, 2003.
7. Moskovitz J and Stadtman ER. Selenium-deficient diet enhances protein oxidation and affects methionine sulfoxide reductase (MsrB) protein level in certain mouse tissues. *Proc Natl Acad Sci USA* 100: 7486–7490, 2003.
8. Novoselov SV, Kim HY, Hua D, Lee BC, Astle CM, Harrison DE, Friguet B, Moustafa ME, Carlson BA, Hatfield DL, and Gladyshev VN. Regulation of selenoproteins and methionine sulfoxide reductases A and B1 by age, calorie restriction, and dietary selenium in mice. *Antioxid Redox Signal* 12: 829–838, 2010.
9. Papp LV, Lu J, Bolderson E, Boucher D, Singh R, Holmgren A, and Khanna KK. SECIS-binding protein 2 promotes cell survival by protecting against oxidative stress. *Antioxid Redox Signal* 12: 797–808, 2010.
10. Papp LV, Lu J, Holmgren A, and Khanna KK. From selenium to selenoproteins: synthesis, identity, and their role in human health. *Antioxid Redox Signal* 9: 775–806, 2007.
11. Reeves MA, Bellinger FP, and Berry MJ. The neuroprotective functions of selenoprotein M and its role in cytosolic calcium regulation. *Antioxid Redox Signal* 12: 809–818, 2010.
12. Arbogast S and Ferreiro A. Selenoproteins and protection against oxidative stress: selenoprotein N as a novel player at the crossroads of redox signaling and calcium homeostasis. *Antioxid Redox Signal* 12: 893–904, 2010.
13. Selenius M, Rundlöf AK, Olm E, Fernandes AP, and Björnstedt M. Selenium and the selenoprotein thioredoxin reductase in the prevention, treatment and diagnostics of cancer. *Antioxid Redox Signal* 12: 867–880, 2010.
14. Shchedrina VA, Zhang Y, Labunskyy VM, Hatfield DL, and Gladyshev VN. Structure–function relations, physiological roles, and evolution of mammalian ER-resident selenoproteins. *Antioxid Redox Signal* 12: 839–849, 2010.
15. Sultana R, Perluigi M, and Butterfield DA. Protein oxidation and lipid peroxidation in brain of subjects with Alzheimer disease: insights into mechanism of neurodegeneration from redox proteomics. *Antioxid Redox Signal* 8: 2021–2037, 2006.
16. Yoo MH, Gu X, Xu XM, Kim JY, Carlson BA, Patterson AD, Cai H, Gladyshev VN, and Hatfield DL. Delineating the role of glutathione peroxidase 4 in protecting cells against lipid hydroperoxide damage and in Alzheimer's disease. *Antioxid Redox Signal* 12: 819–827, 2010.

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1. Aldwin Suryo Rahmanto, David I. Pattison, Michael J. Davies. 2012. Photo-oxidation-induced inactivation of the selenium-containing protective enzymes thioredoxin reductase and glutathione peroxidase. *Free Radical Biology and Medicine* **53**:6, 1308-1316. [CrossRef]
2. Anne Röseler , Judith Helena Prieto , Rimma Iozef , Beate Hecker , Rolf Heiner Schirmer , Simone Külzer , Jude Przyborski , Stefan Rahlfs , Katja Becker . 2012. Insight into the Selenoproteome of the Malaria Parasite Plasmodium falciparum. *Antioxidants & Redox Signaling* **17**:4, 534-543. [Abstract] [Full Text HTML] [Full Text PDF] [Full Text PDF with Links] [Supplemental material]
3. Yan-Hui Han, Zi-Wei Zhang, Jian Su, Bo Zhang, Shu Li, Shi-Wen Xu. 2012. Effects of Chicken Selenoprotein W on H2O2-Induced Apoptosis in CHO-K1 Cells. *Biological Trace Element Research* **147**:1-3, 395-402. [CrossRef]
4. Heiner K. Berthold, Bernhard Michalke, Wilhelm Krone, Eliseo Guallar, Ioanna Gouni-Berthold. 2012. Influence of serum selenium concentrations on hypertension. *Journal of Hypertension* 1. [CrossRef]
5. Norman Metanis, Joris Beld, Donald HilvertThe Chemistry of Selenocysteine . [CrossRef]
6. Aldwin Suryo Rahmanto, Michael J. Davies. 2011. Catalytic activity of selenomethionine in removing amino acid, peptide, and protein hydroperoxides. *Free Radical Biology and Medicine* . [CrossRef]
7. Karin Ljung, Brita Palm, Margaretha Grandér, Marie Vahter. 2011. High concentrations of essential and toxic elements in infant formula and infant foods – A matter of concern. *Food Chemistry* **127**:3, 943-951. [CrossRef]
8. Barron Emmanuelle, Migeot Virginie, Séby Fabienne, Ingrand Isabelle, Potin-Gautier Martine, Legube Bernard, Rabouan Sylvie. 2011. Selenium exposure in subjects living in areas with high selenium concentrated drinking water: Results of a French integrated exposure assessment survey. *Environment International* . [CrossRef]
9. Liping Fu, Qiong Liu, Liming Shen, Yong Wang. 2011. Proteomic study on sodium selenite-induced apoptosis of human cervical cancer HeLa cells. *Journal of Trace Elements in Medicine and Biology* . [CrossRef]
10. F.C. Costa, M.A.V. Oliva, T.C.L. de Jesus, S. Schenkman, O.H. Thiemann. 2011. Oxidative stress protection of Trypanosomes requires selenophosphate synthase. *Molecular and Biochemical Parasitology* . [CrossRef]
11. Min-Hsiung Pan, Huei-Mei Hong, Chih-Li Lin, Ai-Zhi Jhang, Jie-Heng Tsai, Vladimir Badmaev, Kalyanam Nagabhushanam, Chi-Tang Ho, Wei-Jen Chen. 2011. Se-methylselenocysteine inhibits lipopolysaccharide-induced NF-#B activation and iNOS induction in RAW 264.7 murine macrophages. *Molecular Nutrition & Food Research* **55**:5, 723-732. [CrossRef]