

Selenoproteins

Subjects: **Cell Biology**

Contributor: Byung Cheon Lee

Selenium is a vital trace element present as selenocysteine (Sec) in proteins that are, thus, known as selenoproteins. Humans have 25 selenoproteins, most of which are functionally characterized as oxidoreductases, where the Sec residue plays a catalytic role in redox regulation and antioxidant activity. Glutathione peroxidase plays a pivotal role in scavenging and inactivating hydrogen and lipid peroxides, whereas thioredoxin reductase reduces oxidized thioredoxins as well as non-disulfide substrates, such as lipid hydroperoxides and hydrogen peroxide. Selenoprotein R protects the cell against oxidative damage by reducing methionine-R-sulfoxide back to methionine. Selenoprotein O regulates redox homeostasis with catalytic activity of protein AMPylation. Moreover, endoplasmic reticulum (ER) membrane selenoproteins (SelL, K, N, S, and Sel15) are involved in ER membrane stress regulation. Selenoproteins containing the CXXU motif (SelH, M, T, V, and W) are putative oxidoreductases that participate in various cellular processes depending on redox regulation.

selenoprotein

oxidative stress

redox signaling

redox homeostasis

antioxidant

1. Introduction

Most reactive oxygen species (ROS) are generated as by-products of cellular redox processes, including mitochondrial respiration and are known to be harmful to human health when their cellular levels exceed the physiologically acceptable level. However, moderate ROS concentrations play a crucial role in regulating signal transduction and cellular functions, such as proliferation and differentiation, via protein oxidation [1]. Nevertheless, ROS are toxic and can damage various biological molecules, such as proteins, lipids, and nucleic acids. Thus, the imbalance between ROS production and antioxidant capability of the organism is often associated with the development of various chronic pathologies, including cancer, cardiovascular diseases (CVDs), diabetes, neurological disorders, ischemia/reperfusion injury, age-related alterations, dysfunctions related to immune defense and inflammatory responses, and other diseases [1][2][3][4][5][6][7][8][9][10][11].

Antioxidant enzymes such as superoxide dismutase, catalase, and other redox enzymes, including selenoproteins, and low weight antioxidant molecules such as carotenoids, ascorbate, vitamin E, α -lipoic acid, and glutathione (GSH) are essential for maintaining the “steady state” concentration of ROS, which helps to regulate the redox balance and maintain cellular homeostasis. Most functionally characterized selenoproteins have catalytic activities owing to their selenocysteine (Sec) residue and act to neutralize and remove ROS. Therefore, they protect against oxidative stress. Selenium was considered a toxic element for humans and other mammals but is now considered an important trace element, as the benefits of dietary selenium supplementation have been identified [12]. Selenium is widely distributed in various tissues and organs after absorption and performs important biological functions

through regulating the synthesis of selenoproteins and being incorporated in selenoproteins [13]. Furthermore, some selenoproteins are also involved in regulating the activation of signaling pathways and cellular functions. In this review, we provide a brief overview of the various functions of selenoproteins and their roles in redox regulation and physiological functions.

2. Selenocysteine in Selenoproteins

Sulfur and selenium have similar physicochemical properties as both are members of the chalcogen group and undergo thiol-disulfide exchange reactions in the form of cysteine (Cys) or Sec, respectively [14]. However, Sec is more reactive than Cys under physiological conditions as it has a lower pKa (~5.2) than Cys (~8.0); thus, it can exist as a nucleophile without electrostatic interactions and, therefore, has enhanced catalytic efficiency. The Sec residue in most selenoproteins is located in the catalytic region, where it catalyzes the reduction of oxidized Cys residues, such as disulfide and sulfenic acid [15]. Studies have shown that removal of the Sec residues by oxidative selenium elimination, limited proteolysis [16], as well as specific alkylation of the Sec residues at pH 6.5 [16][17], leads to catalytic activity decrease. Moreover, the substitution of Sec with Cys also results in a marked reduction in catalytic efficiency [18][19][20].

Selenoproteins exist in three kingdoms of life, whereas yeast, fungi, and higher plants lack selenoproteins. Instead, they have alternative cysteine-containing homologs [21]. Sec is the 21st amino acid encoded by the in-frame UGA codon, which is usually recognized as a stop codon; therefore, it requires specialized machinery for its incorporation into proteins. This machinery comprises a selenocysteine tRNA (Sec-tRNA^{[Ser]Sec}), a secondary stem-loop structure named selenocysteine insertion sequence (SECIS), SECIS Binding Protein 2 (SBP2), and other protein factors [22][23]. However, its molecular mechanism remains unclear. For Sec-tRNA^{[Ser]Sec} synthesis, selenium can be intaken from dietary sources, including organic forms such as selenomethionine (Se-Met) and inorganic forms such as selenate and selenite [13]. To utilize selenium from Se-Mets, they are converted to Sec by the trans-selenation pathway similar to the trans-sulfuration pathway for Met. Then Sec is converted to H₂Se by Sec b-lyase [24]. In the case of selenite, it interacts with glutathione and is directly reduced to H₂Se. Both organic and inorganic selenium sources become H₂Se and is then converted to selenophosphate, which reacts with tRNA-bound serinyl residues to produce Sec-tRNA^{[Ser]Sec} [25]. In eukaryotes and archaea, SECIS is located in the 3'-untranslated region (UTR) and interacts with *trans*-acting factors [22][26]. This unique feature of SECIS elements and the in-frame UGA codon has been largely adopted for *in silico* selenoproteome identification in diverse organisms. This is a peculiar feature, considering that another sulfur-containing amino acid Met and Se-Met cannot be distinguished by a Met tRNA, and therefore, Se-Mets are incorporated in proteins randomly [27].

Selenoproteins are essential for survival in many organisms, including humans. For example, prostate epithelium-specific selenocysteine tRNA gene *Trsp* deletion leads to oxidative stress, early-onset intraepithelial neoplasia [28], and early embryonic death in mice [29]. Moreover, mammary gland-specific *Trsp* knockout (KO) mice showed that p53 and BRCA1 expression changed, resulting in enhancing susceptibility to cancer [30], which indicates that selenoproteins are essential for mammals. Based on Sec residue localization, selenoproteins can be divided into two groups. In the first group, which includes all thioredoxin reductases (TrxRs) and selenoprotein I (SelI), SelK,

SelO, SelR, and SelS, the Sec residue is located in the C-terminal region. The second group, which contains the rest of the selenoproteins (glutathione peroxidases, iodothyronine deiodinases, SelH, SelM, SelN, SelT, SelV, SelW, SPS2, and Sep15), is characterized by the presence of the Sec residue in the N-terminal region, as part of the redox-active thioredoxin (Trx)-like selenylsulfide/selenolthiol motif [31]. SelP has an N-terminal redox Sec and multiple C-terminal Sec residues [32]. Over half of the mammalian selenoproteins possess the Trx-like fold [33]; its common feature include a two-layer $\alpha/\beta/\alpha$ sandwich structure and a conserved CXXC motif (two Cys residues separated by two other amino acid residues). The CXXC motif is a “rheostat” in the active site [34], because changes in residues that separate the two cysteines influence redox potentials and pKa values of cysteines, configuring proteins for a particular redox function [35]. Altering the CXXC motif affects not only the reduction potential of the protein but also its ability to function as a disulfide isomerase and also affects its interaction with folding protein substrates and reoxidants [20]. The Trx-like fold is commonly observed in proteins, most of which function in disulfide bond formation and isomerization and regulate the redox state of the Cys residues for other functions. Sep15, SelH, SelM, SelO, SelT, SelP, SelW, and SelV contain a CXXU motif, indicating that they have an antioxidant activity, which corresponds to the CXXC motif of the Trx active site. A variety of approaches has been used to determine the biological function of these selenoproteins. However, most selenoproteins (thioredoxin glutathione reductase, SelH, SelI, SelM, SelO, SelT, SelV, SelW) have no known functions. Interestingly, the selenoproteins with identified functions (redox functions) are all oxidoreductases that contain Sec in the catalytic center and participate in various redox processes, such as antioxidant defense, redox signaling, redox regulation of biological functions, and many other processes that regulate intracellular redox homeostasis [31][36][37][38].

3. Selenoprotein R

SelR (also designated as MsrB1) is an antioxidant enzyme that uses Met to defend cellular macromolecules against oxidative stress. Met is a sulfur-containing amino acid that is readily oxidized to Met sulfoxide by ROS; subsequently, Met sulfoxide reductases (Msr) such as SelR reduce Met sulfoxide back to Met [39]. Met sulfoxide contains two diastereomeric forms, Met-S-sulfoxide (Met-S-SO) and Met-R-sulfoxide (Met-R-SO) [40]. Met-R-SO is reduced by the MsrB family of proteins, including SelR, whereas Met-S-SO is reduced by the MsrA family of proteins [41]. Mammals have one MsrA and three MsrBs, namely, SelR, MsrB2, and MsrB3 [18]. Among these, SelR is the only selenoprotein that is localized in both the cytosol and nucleus. SelR is present specifically in vertebrates and appears to have evolved separately, having the lowest homology with other Msr enzymes [42].

SelR expression is regulated by dietary selenium; its mRNA expression level is low in a selenium-deficient diet, but this can be reversed by dietary selenium supplementation [43]. SelR activity was also found to reduce with age [44]. SelR has catalytic activity, especially for protein-bound and free Met-R-SO but has low catalytic efficiency. Like other Msr enzymes, SelR is an oxidoreductase that requires Trx/TrxR/NADPH to recycle its oxidized form to the reduced form (Figure 1A) [45]. Along with its catalytic activity toward protein-bound Met-R-SO, SelR plays a role in repairing oxidized proteins, thus protecting the structure and function of proteins against oxidative stress [46]. SelR also regulates biological processes via the reversible oxidation/reduction of Met residues in proteins. The oxidation of Met residues at certain sites by either ROS or enzymes often leads to changes in protein function, which can

then be reversed by SelR-catalyzed reduction of the said Met residues [47]. For instance, it was found that F-actin disassembly caused by the stereospecific oxidation of the 44 and 47 Met residues in actin by MICL proteins can be rescued by SelR [48]. Actin cytoskeleton dynamics regulation is important for many cellular responses, including neural development, muscle contraction, and filopodia formation [49][50][51]. Moreover, F-actin assembly is known to be bidirectionally associated with the mitogen-activated protein kinase (MAPK) pathway, which controls many cellular processes, including cell proliferation [52]. Accordingly, SelR is a potentially redox-dependent regulator that participates in many cellular processes and signaling pathways related to actin cytoskeleton dynamics via F-actin assembly regulation.

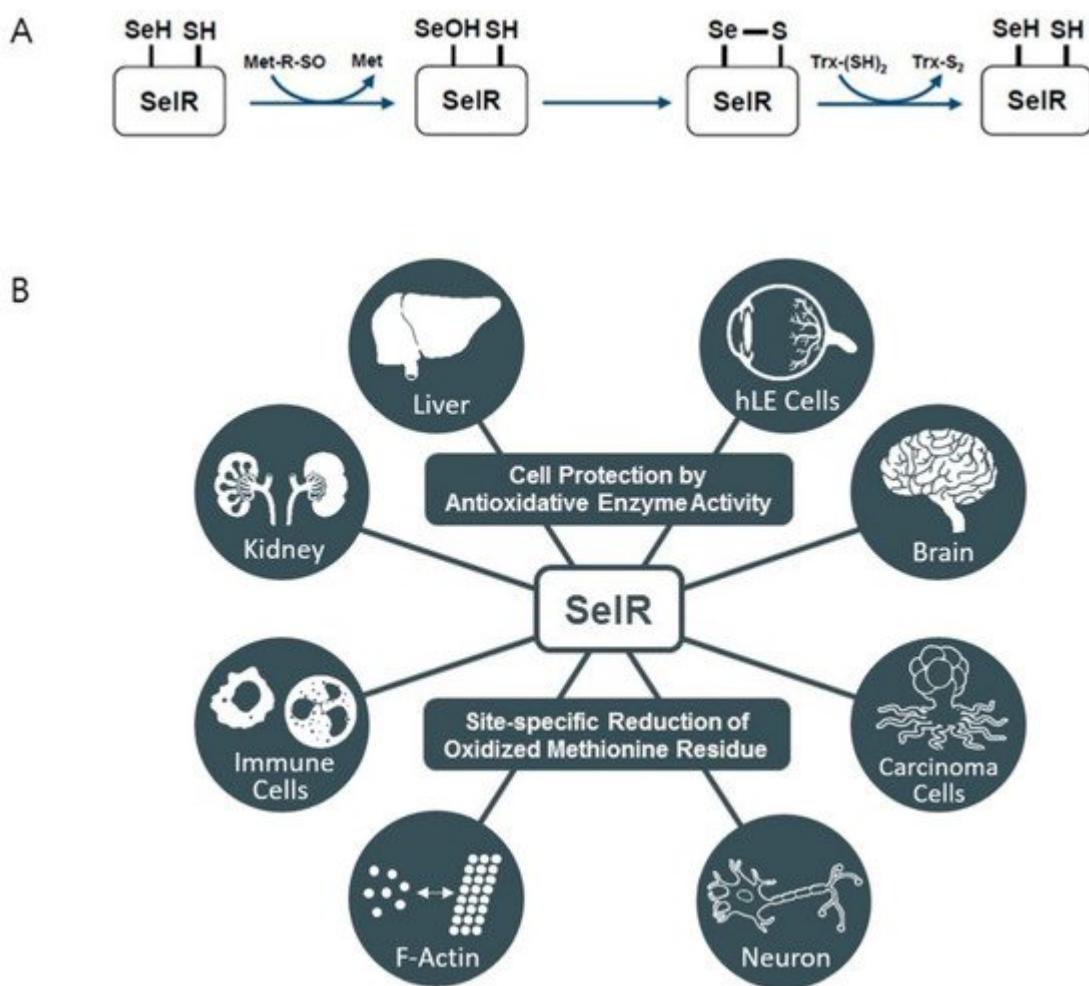


Figure 1. (A) Catalytic mechanism of SelR reducing methionine-R-sulfoxide (Met-R-SO). The catalytic selenocysteine (Sec) residue attacks Met-R-SO and forms the intermediate selenenic acid with Met release. The resolving cysteine (Cys) residue attacks the intermediate, resulting in the formation of intramolecular selenide–sulfide bond. The intramolecular selenide–sulfide bond of SelR is directly reduced by thioredoxin (Trx) system. (B) Role of SelR in various organs and cell types.

SelR KO mice exhibit increased oxidative stress in the liver and kidney with exacerbated hepatotoxicity [53][54]. SelR is also required for human lens epithelial (hLE) cell viability against oxidative stress-induced apoptosis and attenuates cataracts [55]. Since membrane-bound proteins in hLE cells from patients with cataract contain high

levels of Met sulfoxide residues, SelR may directly retard cataract [56]. SelR appears to play an important role in innate immunity; however, its underlying mechanism is poorly understood. In macrophages, SelR expression is induced by lipopolysaccharides and is involved in controlling macrophage function by promoting the expression of anti-inflammatory cytokines, such as IL-10 and IL-1RA [57]. Neutrophils were also shown to have high levels of SelR expression in response to excessive ROS. Moreover, a recent study has suggested that decreased SelR activity in neutrophils might be associated with AD [58]. A study has also shown that SelR is highly expressed in carcinoma cells in response to increased oxidative stress, and may thus enhance carcinoma cell survival. Moreover, SelR expression upregulation aggravates oncogenesis by promoting proliferation via MAPK pathway activation and promotes invasion and metastasis by regulating actin cytoskeleton dynamics [59][60] (Figure 1B).

4. Selenoprotein O

SelO, the largest protein among the 25 mammalian selenoproteins, is expressed in a variety of organs, such as the brain, heart, liver, kidneys, lungs, and stomach [61][62]. Unlike SelR and GPx1 expression, SelO expression is not influenced by a selenium-deficient diet [62]. In higher eukaryotes, SelO contains a single Sec residue near the C-terminal region [61][62]. Notably, in lower eukaryotes and all prokaryotes, the Sec residue in SelO is replaced with an invariant Cys residue [63]. Mammalian SelO is located in the mitochondria [62][63], and the occurrence of the CXXU motif in the C-terminal region suggests that SelO might have a redox-active Sec residue, similar to other thiol-dependent oxidoreductases [62]. SelO activity in *Escherichia coli* is regulated by intramolecular disulfide bridge formation between a Cys residue in the activation loop (Cys272) and the Cys residue in the C-terminal region (Cys476), with the latter being replaced by a Sec residue in higher eukaryotes [63]. Using bioinformatic tools, Dudkiewicz et al. predicted that the three-dimensional structure of SelO may be similar to that of a protein kinase and that it might have phosphotransferase activity [64]. Recently, structural studies have shown that SelO is a highly conserved pseudokinase that transfers AMP from ATP to Ser, Thr, and Tyr residues in its substrate protein via a process known as AMPylation [63]. SelO plays a role in response to oxidative stress and regulates global S-glutathionylation levels via AMPylation in conjunction with glutaredoxin [63] (Figure 2). Furthermore, SelO has been shown to play an essential role in chondrocyte viability, proliferation, and chondrogenic differentiation [65]. However, the physiological functions of SelO remain unknown. As such, further research is needed to clarify its physiological functions, role in disease, and association with other redox enzymes.

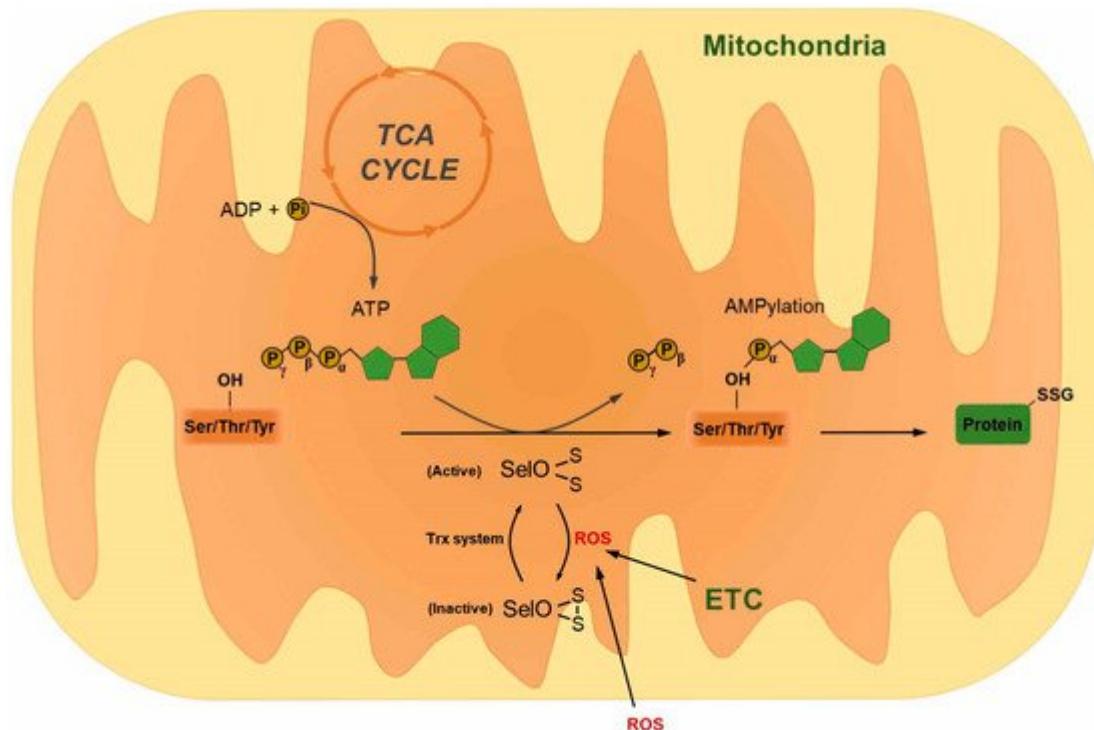


Figure 2. Selenoprotein O (SelO) mediates protein AMPylation and protects the cell from oxidative stress.

References

1. Valko, M.; Rhodes, C.J.; Moncol, J.; Izakovic, M.; Mazur, M. Free radicals, metals and antioxidants in oxidative stress-induced cancer. *Chem. Biol. Interact.* 2006, 160, 1–40.
2. Valko, M.; Leibfritz, D.; Moncol, J.; Cronin, M.T.; Mazur, M.; Telser, J. Free radicals and antioxidants in normal physiological functions and human disease. *Int. J. Biochem. Cell Biol.* 2007, 39, 44–84.
3. Dalle-Donne, I.; Rossi, R.; Colombo, R.; Giustarini, D.; Milzani, A. Biomarkers of oxidative damage in human disease. *Clin. Chem.* 2006, 52, 601–623.
4. Dhalla, N.S.; Temsah, R.M.; Netticadan, T. Role of oxidative stress in cardiovascular diseases. *J. hypertens.* 2000, 18, 655–673.
5. Jenner, P. Oxidative stress in Parkinson's disease. *Ann. Neurol.* 2003, 53 (Suppl. 3), S26–S36; discussion S36–S38.
6. Sayre, L.M.; Smith, M.A.; Perry, G. Chemistry and biochemistry of oxidative stress in neurodegenerative disease. *Curr. Med. Chem.* 2001, 8, 721–738.
7. Brownlee, M.; Cerami, A. The biochemistry of the complications of diabetes mellitus. *Annu. Rev. Biochem.* 1981, 50, 385–432.

8. Kasparova, S.; Brezova, V.; Valko, M.; Horecky, J.; Mlynarik, V.; Liptaj, T.; Vancova, O.; Ulicna, O.; Dobrota, D. Study of the oxidative stress in a rat model of chronic brain hypoperfusion. *Neurochem. Int.* 2005, 46, 601–611.
9. Harman, D. Aging: A theory based on free radical and radiation chemistry. *J. gerontol.* 1956, 11, 298–300.
10. Choi, S.M.; Kim, D.-H.; Chun, K.-S.; Choi, J.-S. Carnosol induces apoptotic cell death through ROS-dependent inactivation of STAT3 in human melanoma G361 cells. *Appl. Biol. Chem.* 2019, 62.
11. Utaipan, T.; Boonyanuphong, P.; Chuprajob, T.; Suksamrarn, A.; Chunglok, W. A trienone analog of curcumin, 1,7-bis(3-hydroxyphenyl)-1,4,6-heptatrien-3-one, possesses ROS- and caspase-mediated apoptosis in human oral squamous cell carcinoma cells in vitro. *Appl. Biol. Chem.* 2020, 63.
12. Avery, J.C.; Hoffmann, P.R. Selenium, Selenoproteins, and Immunity. *Nutrients* 2018, 10, 1203.
13. Wang, N.; Tan, H.Y.; Li, S.; Xu, Y.; Guo, W.; Feng, Y. Supplementation of Micronutrient Selenium in Metabolic Diseases: Its Role as an Antioxidant. *Oxid. Med. Cell Longev.* 2017, 2017, 7478523.
14. Wessjohann, L.A.; Schneider, A.; Abbas, M.; Brandt, W. Selenium in chemistry and biochemistry in comparison to sulfur. *Biol. Chem.* 2007, 388, 997–1006.
15. Lobanov, A.V.; Hatfield, D.L.; Gladyshev, V.N. Eukaryotic selenoproteins and selenoproteomes. *Biochim. et biophys. acta* 2009, 1790, 1424–1428.
16. Gromer, S.; Wissing, J.; Behne, D.; Ashman, K.; Schirmer, R.H.; Flohe, L.; Becker, K. A hypothesis on the catalytic mechanism of the selenoenzyme thioredoxin reductase. *Biochem. J.* 1998, 332, 591–592.
17. Gorlatov, S.N.; Stadtman, T.C. Human selenium-dependent thioredoxin reductase from HeLa cells: Properties of forms with differing heparin affinities. *Arch. Biochem. Biophys.* 1999, 369, 133–142.
18. Chung, S.S.; Kim, M.; Youn, B.S.; Lee, N.S.; Park, J.W.; Lee, I.K.; Lee, Y.S.; Kim, J.B.; Cho, Y.M.; Lee, H.K.; et al. Glutathione peroxidase 3 mediates the antioxidant effect of peroxisome proliferator-activated receptor gamma in human skeletal muscle cells. *Mol. Cell. Biol.* 2009, 29, 20–30.
19. Lee, S.R.; Bar-Noy, S.; Kwon, J.; Levine, R.L.; Stadtman, T.C.; Rhee, S.G. Mammalian thioredoxin reductase: Oxidation of the C-terminal cysteine/selenocysteine active site forms a thioselenide, and replacement of selenium with sulfur markedly reduces catalytic activity. *Proc. Natl. Acad. Sci. USA* 2000, 97, 2521–2526.

20. Quan, S.; Schneider, I.; Pan, J.; Von Hacht, A.; Bardwell, J.C. The CXXC motif is more than a redox rheostat. *J. Biol. Chem.* 2007, 282, 28823–28833.

21. Johansson, L.; Gafvelin, G.; Arner, E.S. Selenocysteine in proteins-properties and biotechnological use. *Biochim. biophy. Acta* 2005, 1726, 1–13.

22. Berry, M.J.; Banu, L.; Chen, Y.Y.; Mandel, S.J.; Kieffer, J.D.; Harney, J.W.; Larsen, P.R. Recognition of UGA as a selenocysteine codon in type I deiodinase requires sequences in the 3' untranslated region. *Nature* 1991, 353, 273–276.

23. Bellinger, F.P.; Raman, A.V.; Reeves, M.A.; Berry, M.J. Regulation and function of selenoproteins in human disease. *Biochem. J.* 2009, 422, 11–22.

24. Mattmiller, S.A.; Carlson, B.A.; Sordillo, L.M. Regulation of inflammation by selenium and selenoproteins: Impact on eicosanoid biosynthesis. *J. Nutr. Sci.* 2013, 2, e28.

25. Fairweather-Tait, S.J.; Collings, R.; Hurst, R. Selenium bioavailability: Current knowledge and future research requirements. *Am. J. Clin. Nutr.* 2010, 91, 1484S–1491S.

26. Hatfield, D.L.; Gladyshev, V.N. How selenium has altered our understanding of the genetic code. *Mol. Cell. Biol.* 2002, 22, 3565–3576.

27. Spallholz, J.E. Selenomethionine and Methioninase: Selenium Free Radical Anticancer Activity. *Methods Mol. Biol.* 2019, 1866, 199–210.

28. Luchman, H.A.; Villemaire, M.L.; Bismar, T.A.; Carlson, B.A.; Jirik, F.R. Prostate epithelium-specific deletion of the selenocysteine tRNA gene Trsp leads to early onset intraepithelial neoplasia. *Am. J. Pathol.* 2014, 184, 871–877.

29. Bosl, M.R.; Takaku, K.; Oshima, M.; Nishimura, S.; Taketo, M.M. Early embryonic lethality caused by targeted disruption of the mouse selenocysteine tRNA gene (Trsp). *Proc. Natl. Acad. Sci. USA* 1997, 94, 5531–5534.

30. Kumaraswamy, E.; Carlson, B.A.; Morgan, F.; Miyoshi, K.; Robinson, G.W.; Su, D.; Wang, S.; Southon, E.; Tessarollo, L.; Lee, B.J.; et al. Selective removal of the selenocysteine tRNA [Ser]Sec gene (Trsp) in mouse mammary epithelium. *Mol. Cell. Biol.* 2003, 23, 1477–1488.

31. Papp, L.V.; Lu, J.; Holmgren, A.; Khanna, K.K. From selenium to selenoproteins: Synthesis, identity, and their role in human health. *Antioxid. Redox Signal.* 2007, 9, 775–806.

32. Burk, R.F.; Hill, K.E. Selenoprotein P: An extracellular protein with unique physical characteristics and a role in selenium homeostasis. *Annu. Rev. Nutr.* 2005, 25, 215–235.

33. Qi, Y.; Grishin, N.V. Structural classification of thioredoxin-like fold proteins. *Proteins* 2005, 58, 376–388.

34. Chivers, P.T.; Prehoda, K.E.; Raines, R.T. The CXXC motif: A rheostat in the active site. *Biochemistry* 1997, 36, 4061–4066.

35. Chivers, P.T.; Laboissiere, M.C.; Raines, R.T. The CXXC motif: Imperatives for the formation of native disulfide bonds in the cell. *EMBO J.* 1996, 15, 2659–2667.

36. Reeves, M.A.; Hoffmann, P.R. The human selenoproteome: Recent insights into functions and regulation. *Cell. Mol. Life Sci.* 2009, 66, 2457–2478.

37. Lee, B.C.; Peterfi, Z.; Hoffmann, F.W.; Moore, R.E.; Kaya, A.; Avanesov, A.; Tarrago, L.; Zhou, Y.; Weerapana, E.; Fomenko, D.E.; et al. MsrB1 and MICALs regulate actin assembly and macrophage function via reversible stereoselective methionine oxidation. *Mol. Cell.* 2013, 51, 397–404.

38. Hawkes, W.C.; Alkan, Z. Regulation of redox signaling by selenoproteins. *Biol. Trace Elem. Res.* 2010, 134, 235–251.

39. Martinez, Y.; Li, X.; Liu, G.; Bin, P.; Yan, W.; Mas, D.; Valdivie, M.; Hu, C.A.; Ren, W.; Yin, Y. The role of methionine on metabolism, oxidative stress, and diseases. *Amino Acids.* 2017, 49, 2091–2098.

40. Bin, P.; Huang, R.; Zhou, X. Oxidation Resistance of the Sulfur Amino Acids: Methionine and Cysteine. *Biomed. Res. Int.* 2017, 2017, 9584932.

41. Jiang, B.; Moskovitz, J. The Functions of the Mammalian Methionine Sulfoxide Reductase System and Related Diseases. *Antioxidants* 2018, 7, 122.

42. Hansel, A.; Heinemann, S.H.; Hoshi, T. Heterogeneity and function of mammalian MSRs: Enzymes for repair, protection and regulation. *J. Nutr. Biochem.* 2005, 1703, 239–247.

43. Cao, L.; Zhang, L.; Zeng, H.; Wu, R.T.; Wu, T.L.; Cheng, W.H. Analyses of Selenotranscriptomes and Selenium Concentrations in Response to Dietary Selenium Deficiency and Age Reveal Common and Distinct Patterns by Tissue and Sex in Telomere-Dysfunctional Mice. *J. Nutr.* 2017, 147, 1858–1866.

44. Novoselov, S.V.; Kim, H.-Y.; Hua, D.; Lee, B.C.; Astle, C.M.; Harrison, D.E.; Friguet, B.; Moustafa, M.E.; Carlson, B.A.; Hatfield, D.L. Regulation of selenoproteins and methionine sulfoxide reductases A and B1 by age, calorie restriction, and dietary selenium in mice. *Antioxid. Redox Signal.* 2010, 12, 829–838.

45. Gladyshev, V.N.; Stadtman, T.C.; Hatfield, D.L.; Jeang, K.T. Levels of major selenoproteins in T cells decrease during HIV infection and low molecular mass selenium compounds increase. *Proc. Natl. Acad. Sci. USA* 1999, 96, 835–839.

46. Lourenço dos Santos, S.; Petropoulos, I.; Friguet, B. The Oxidized Protein Repair Enzymes Methionine Sulfoxide Reductases and Their Roles in Protecting against Oxidative Stress, in

Ageing and in Regulating Protein Function. *Antioxidants* 2018, 7, 191.

47. Kaya, A.; Lee, B.C.; Gladyshev, V.N. Regulation of protein function by reversible methionine oxidation and the role of selenoprotein MsrB1. *Antioxid. Redox Signal.* 2015, 23, 814–822.

48. Hung, R.J.; Spaeth, C.S.; Yesilyurt, H.G.; Terman, J.R. SelR reverses Mical-mediated oxidation of actin to regulate F-actin dynamics. *Nat. Cell. Biol.* 2013, 15, 1445–1454.

49. Kawabata Galbraith, K.; Kengaku, M. Multiple roles of the actin and microtubule-regulating formins in the developing brain. *Neurosci. Res.* 2019, 138, 59–69.

50. Tang, D.D. The Dynamic Actin Cytoskeleton in Smooth Muscle. *Adv. Pharmacol.* 2018, 81, 1–38.

51. Gallop, J.L. Filopodia and their links with membrane traffic and cell adhesion. *Semin. Cell. Dev. Biol.* 2019.

52. Leinweber, B.D.; Leavis, P.C.; Grabarek, Z.; Wang, C.-L.A.; Morgan, K.G. Extracellular regulated kinase (ERK) interaction with actin and the calponin homology (CH) domain of actin-binding proteins. *Biochem. J.* 1999, 344, 117–123.

53. Fomenko, D.E.; Novoselov, S.V.; Natarajan, S.K.; Lee, B.C.; Koc, A.; Carlson, B.A.; Lee, T.H.; Kim, H.Y.; Hatfield, D.L.; Gladyshev, V.N. MsrB1 (methionine-R-sulfoxide reductase 1) knock-out mice: Roles of MsrB1 in redox regulation and identification of a novel selenoprotein form. *J. Biol. Chem.* 2009, 284, 5986–5993.

54. Kim, K.Y.; Kwak, G.H.; Singh, M.P.; Gladyshev, V.N.; Kim, H.Y. Selenoprotein MsrB1 deficiency exacerbates acetaminophen-induced hepatotoxicity via increased oxidative damage. *Arch. Biochem. Biophys.* 2017, 634, 69–75.

55. Jia, Y.; Zhou, J.; Liu, H.; Huang, K. Effect of methionine sulfoxide reductase B1 (SelR) gene silencing on peroxynitrite-induced F-actin disruption in human lens epithelial cells. *Biochem. Biophys. Res. Commun.* 2014, 443, 876–881.

56. Dai, J.; Liu, H.; Zhou, J.; Huang, K. Selenoprotein R Protects Human Lens Epithelial Cells against D-Galactose-Induced Apoptosis by Regulating Oxidative Stress and Endoplasmic Reticulum Stress. *Int. J. Mol. Sci.* 2016, 17, 231.

57. Lee, B.C.; Lee, S.G.; Choo, M.K.; Kim, J.H.; Lee, H.M.; Kim, S.; Fomenko, D.E.; Kim, H.Y.; Park, J.M.; Gladyshev, V.N. Selenoprotein MsrB1 promotes anti-inflammatory cytokine gene expression in macrophages and controls immune response in vivo. *Sci. Rep.* 2017, 7, 5119.

58. Achilli, C.; Ciana, A.; Minetti, G. Brain, immune system and selenium: A starting point for a new diagnostic marker for Alzheimer's disease? *Oxid. Med. Cell. Longev.* 2018, 138, 223–226.

59. He, Q.; Li, H.; Meng, F.; Sun, X.; Feng, X.; Chen, J.; Li, L.; Liu, J. Methionine Sulfoxide Reductase B1 Regulates Hepatocellular Carcinoma Cell Proliferation and Invasion via the Mitogen-Activated

Protein Kinase Pathway and Epithelial-Mesenchymal Transition. *Oxid. Med. Cell. Longev.* 2018, 2018, 5287971.

60. Li, H.; He, Q.; Meng, F.; Feng, X.; Chen, J.; Li, L.; Liu, J. Methionine sulfoxide reductase B1 regulates proliferation and invasion by affecting mitogen-activated protein kinase pathway and epithelial-mesenchymal transition in u2os cells. *Biochem. Biophys. Res. Commun.* 2018, 496, 806–813.
61. Kryukov, G.V.; Castellano, S.; Novoselov, S.V.; Lobanov, A.V.; Zehtab, O.; Guigo, R.; Gladyshev, V.N. Characterization of mammalian selenoproteomes. *Science* 2003, 300, 1439–1443.
62. Han, S.J.; Lee, B.C.; Yim, S.H.; Gladyshev, V.N.; Lee, S.R. Characterization of mammalian selenoprotein o: A redox-active mitochondrial protein. *PLoS One* 2014, 9, e95518.
63. Sreelatha, A.; Yee, S.S.; Lopez, V.A.; Park, B.C.; Kinch, L.N.; Pilch, S.; Servage, K.A.; Zhang, J.; Jiou, J.; Karasiewicz-Urbanska, M.; et al. Protein AMPylation by an Evolutionarily Conserved Pseudokinase. *Cell* 2018, 175, 809–821.e819.
64. Dudkiewicz, M.; Szczeplinska, T.; Grynberg, M.; Pawlowski, K. A novel protein kinase-like domain in a selenoprotein, widespread in the tree of life. *PLoS One* 2012, 7, e32138.
65. Yan, J.; Fei, Y.; Han, Y.; Lu, S. Selenoprotein O deficiencies suppress chondrogenic differentiation of ATDC5 cells. *Cell Biol. Int.* 2016.

Retrieved from <https://encyclopedia.pub/entry/history/show/24777>