1. Phylogeny  
   Selenoprotein O (SELENOO), also known as SELO, is widely conserved across the domains of life, with orthologs found in bacteria, yeast, plants, and mammals (chaudiere2023biologicalandcatalytic pages 20-21, dudkiewicz2012anovelprotein pages 1-2). Within metazoans, SELENOO is predominantly encoded as a single-copy gene, although gene duplications have been noted in some lineages, reflecting an evolutionarily ancient origin. The protein belongs to the pseudokinase superfamily and harbors a kinase‐like domain that, despite divergence in classical catalytic residues, retains structural features common to other atypical kinases (dudkiewicz2012anovelprotein pages 3-4). Phylogenetic analyses place SELENOO among a core set of kinases present since the emergence of eukaryotes, indicating that its conserved protein kinase fold has been maintained across evolution to support essential mitochondrial functions (tsuji2021historicalrolesof pages 8-9).
2. Reaction Catalyzed  
   SELENOO catalyzes an adenylyltransferase reaction, whereby an adenosine 5′-monophosphate (AMP) moiety is transferred from ATP to the hydroxyl groups of serine, threonine, or tyrosine residues in substrate proteins. This AMPylation reaction can be summarized as follows:  
     ATP + [protein]–OH → [protein]–AMP + PP\_i  
   This chemical transformation distinguishes SELENOO from canonical phosphoryl transferases, as it does not result in phosphorylation but in the covalent attachment of AMP to target proteins (chaudiere2023biologicalandcatalytic pages 20-21, mukherjee2022identificationofselenoprotein pages 1-3).
3. Cofactor Requirements  
   The catalytic activity of SELENOO is dependent on ATP as the donor of the AMP moiety. In analogy with other protein kinases, the coordination of ATP is facilitated by divalent cations, with Mg²⁺ being the most common cofactor implicated in nucleotide binding and orientation within the active site. Although detailed experimental reports on metal ion requirements for SELENOO are limited, the structural and enzymological characteristics of its kinase‐like domain strongly suggest that Mg²⁺ is necessary to support its ATP‐dependent AMPylation reaction (chaudiere2023biologicalandcatalytic pages 20-21, dudkiewicz2012anovelprotein pages 4-6).
4. Substrate Specificity  
   SELENOO exhibits broad substrate specificity by targeting the hydroxyl side chains of serine, threonine, and tyrosine residues. A known substrate is glutaredoxin, a protein involved in the reversible S-glutathionylation of other proteins, thereby integrating redox regulation with post-translational modification (chaudiere2023biologicalandcatalytic pages 20-21). Although a detailed consensus motif for SELENOO substrate recognition has not yet been definitively established, its kinase‐like domain mediates AMPylation with a preference for these residues. Advanced mapping studies using biotinylated ATP analogs have been employed to enrich and identify AMPylated substrates, supporting the notion that SELENOO’s substrate specificity is functionally linked to redox regulatory pathways (mukherjee2022identificationofselenoprotein pages 13-16, tsuji2021historicalrolesof pages 8-9).
5. Structure  
   SELENOO is a large mitochondrial selenoprotein of approximately 73 kDa that features a prominent kinase‐like domain. The domain organization comprises an N‐terminal region lacking well‐defined structural motifs, a central kinase‐like domain spanning roughly residues 120–470, and a C‐terminal region that contains a highly conserved redox-active motif—typically a C–x–x–U sequence, where U denotes selenocysteine. The central domain adopts a bilobal architecture reminiscent of classical protein kinases, with a smaller N‐terminal lobe primarily involved in ATP binding and a larger C‐terminal lobe that likely accommodates substrate interactions and catalysis. Key catalytic features of the kinase‐like domain include a conserved lysine that coordinates ATP, an activation loop and hydrophobic spines that support conformational integrity, and a non‐canonical substitution for the typical catalytic aspartate residue found in conventional kinases (dudkiewicz2012anovelprotein pages 4-6, dogaru2023“alphabet”selenoproteinstheir pages 3-4). Although no crystallographic structure for human SELENOO is currently available, computational predictions—such as those predicted by AlphaFold—support the overall kinase‐like fold with these distinctive features, underscoring its role in atypical AMPylation rather than canonical phosphorylation (chaudiere2023biologicalandcatalytic pages 20-21, dudkiewicz2012anovelprotein pages 12-13).
6. Regulation  
   The activity of SELENOO is subject to regulation by the cellular redox state. AMPylation activity has been shown to depend on the reduction of an intramolecular disulfide bond, which, when reduced, permits proper catalytic activity. Consequently, the enzyme is thought to act as a redox sensor within mitochondria, with its activity being modulated by the oxidative environment. Although specific post-translational modifications such as phosphorylation or ubiquitination have not been definitively mapped for SELENOO, its regulation appears to be tightly linked to the redox conditions that impact its disulfide bond status and, by extension, its conformation and enzymatic function (chaudiere2023biologicalandcatalytic pages 20-21, tsuji2021historicalrolesof pages 8-9).
7. Function  
   SELENOO functions primarily as an AMPylating enzyme within mitochondria, where its catalytic activity plays a role in redox regulation. By transferring AMP to serine, threonine, or tyrosine residues on target proteins, SELENOO modulates the activity of these proteins—one well-characterized example being glutaredoxin, which is involved in the dynamic regulation of protein S-glutathionylation. Through this post-translational modification, SELENOO contributes to the maintenance of cellular redox homeostasis and the protection of cells against oxidative stress. The mitochondrial localization of SELENOO, together with its evolutionary conservation, underscores its functional significance in controlling redox signalling pathways that are critical for cellular metabolism and potentially for processes such as chondrogenic differentiation (zhang2020roleofselenoproteins pages 7-9, chaudiere2023biologicalandcatalytic pages 20-21).
8. Other Comments  
   Currently, no specific inhibitors for SELENOO have been well established in the literature. While the enzyme’s AMPylation activity and redox regulatory role suggest potential involvement in oxidative stress-related pathologies and mitochondrial dysfunction, explicit disease associations and the impact of defined mutations in SELENOO remain under investigation. Given its integration within the mitochondrial redox network and its unique catalytic mechanism that diverges from conventional phosphorylation, SELENOO represents a promising target for further studies that may elucidate its role in human disease. Experimental approaches employing ATP analogs and redox-sensitive assays have been developed to better characterize SELENOO’s substrate repertoire and regulatory mechanisms (reeves2009thehumanselenoproteome pages 8-9, zoidis2018seleniumdependentantioxidantenzymes pages 13-15).
9. References
10. Chaudière, J. (2023). Biological and catalytic properties of selenoproteins. International Journal of Molecular Sciences, Jun 2023, pages 20-21.
11. Dudkiewicz, M., Szczepińska, T., Grynberg, M., & Pawłowski, K. (2012). A novel protein kinase-like domain in a selenoprotein, widespread in the tree of life. PLoS ONE, Feb 2012, pages 1-2, 3-4, 4-6, 12-13.
12. Reeves, M. A. & Hoffmann, P. R. (2009). The human selenoproteome: recent insights into functions and regulation. Cellular and Molecular Life Sciences, Apr 2009, pages 8-9.
13. Zhang, Y. et al. (2020). Role of selenoproteins in redox regulation of signaling and the antioxidant system: a review. Antioxidants, May 2020, pages 7-9.
14. Zoidis, E., Seremelis, I., Kontopoulos, N., & Danezis, G. (2018). Selenium-dependent antioxidant enzymes: actions and properties of selenoproteins. Antioxidants, May 2018, pages 13-15.
15. Dogaru, C. et al. (2023). “Alphabet” selenoproteins: their characteristics and physiological roles. International Journal of Molecular Sciences, Nov 2023, pages 3-4.
16. Mukherjee, M. & Sreelatha, A. (2022). Identification of selenoprotein O substrates using a biotinylated ATP analog. Methods in Enzymology, 2022, pages 1-3, 13-16.
17. Tsuji, P. et al. (2021). Historical roles of selenium and selenoproteins in health and development: the good, the bad and the ugly. International Journal of Molecular Sciences, Dec 2021, pages 8-9.

References

1. (chaudiere2023biologicalandcatalytic pages 20-21): J. Chaudière. Biological and catalytic properties of selenoproteins. International Journal of Molecular Sciences, Jun 2023. URL: https://doi.org/10.3390/ijms241210109, doi:10.3390/ijms241210109. This article has 30 citations and is from a peer-reviewed journal.
2. (dudkiewicz2012anovelprotein pages 1-2): Małgorzata Dudkiewicz, Teresa Szczepińska, Marcin Grynberg, and Krzysztof Pawłowski. A novel protein kinase-like domain in a selenoprotein, widespread in the tree of life. PLoS ONE, 7:e32138, Feb 2012. URL: https://doi.org/10.1371/journal.pone.0032138, doi:10.1371/journal.pone.0032138. This article has 80 citations and is from a peer-reviewed journal.
3. (dudkiewicz2012anovelprotein pages 4-6): Małgorzata Dudkiewicz, Teresa Szczepińska, Marcin Grynberg, and Krzysztof Pawłowski. A novel protein kinase-like domain in a selenoprotein, widespread in the tree of life. PLoS ONE, 7:e32138, Feb 2012. URL: https://doi.org/10.1371/journal.pone.0032138, doi:10.1371/journal.pone.0032138. This article has 80 citations and is from a peer-reviewed journal.
4. (reeves2009thehumanselenoproteome pages 8-9): M. A. Reeves and P. R. Hoffmann. The human selenoproteome: recent insights into functions and regulation. Cellular and Molecular Life Sciences, 66:2457-2478, Apr 2009. URL: https://doi.org/10.1007/s00018-009-0032-4, doi:10.1007/s00018-009-0032-4. This article has 649 citations and is from a domain leading peer-reviewed journal.
5. (zhang2020roleofselenoproteins pages 7-9): Ying Zhang, Y. Roh, Seong-Jeong Han, Iha Park, Hae Min Lee, Y. Ok, B. Lee, and Seung-Rock Lee. Role of selenoproteins in redox regulation of signaling and the antioxidant system: a review. Antioxidants, May 2020. URL: https://doi.org/10.3390/antiox9050383, doi:10.3390/antiox9050383. This article has 221 citations and is from a peer-reviewed journal.
6. (zoidis2018seleniumdependentantioxidantenzymes pages 13-15): Evangelos Zoidis, Isidoros Seremelis, Nikolaos Kontopoulos, and Georgios Danezis. Selenium-dependent antioxidant enzymes: actions and properties of selenoproteins. Antioxidants, 7:66, May 2018. URL: https://doi.org/10.3390/antiox7050066, doi:10.3390/antiox7050066. This article has 452 citations and is from a peer-reviewed journal.
7. (dogaru2023“alphabet”selenoproteinstheir pages 3-4): C. Dogaru, C. Muscurel, C. Duță, and Irina Stoian. “alphabet” selenoproteins: their characteristics and physiological roles. International Journal of Molecular Sciences, Nov 2023. URL: https://doi.org/10.3390/ijms242115992, doi:10.3390/ijms242115992. This article has 20 citations and is from a peer-reviewed journal.
8. (dudkiewicz2012anovelprotein pages 12-13): Małgorzata Dudkiewicz, Teresa Szczepińska, Marcin Grynberg, and Krzysztof Pawłowski. A novel protein kinase-like domain in a selenoprotein, widespread in the tree of life. PLoS ONE, 7:e32138, Feb 2012. URL: https://doi.org/10.1371/journal.pone.0032138, doi:10.1371/journal.pone.0032138. This article has 80 citations and is from a peer-reviewed journal.
9. (dudkiewicz2012anovelprotein pages 3-4): Małgorzata Dudkiewicz, Teresa Szczepińska, Marcin Grynberg, and Krzysztof Pawłowski. A novel protein kinase-like domain in a selenoprotein, widespread in the tree of life. PLoS ONE, 7:e32138, Feb 2012. URL: https://doi.org/10.1371/journal.pone.0032138, doi:10.1371/journal.pone.0032138. This article has 80 citations and is from a peer-reviewed journal.
10. (mukherjee2022identificationofselenoprotein pages 1-3): Meghomukta Mukherjee and Anju Sreelatha. Identification of selenoprotein o substrates using a biotinylated atp analog. Methods in enzymology, 662:275-296, 2022. URL: https://doi.org/10.1016/bs.mie.2021.10.001, doi:10.1016/bs.mie.2021.10.001. This article has 6 citations and is from a peer-reviewed journal.
11. (mukherjee2022identificationofselenoprotein pages 13-16): Meghomukta Mukherjee and Anju Sreelatha. Identification of selenoprotein o substrates using a biotinylated atp analog. Methods in enzymology, 662:275-296, 2022. URL: https://doi.org/10.1016/bs.mie.2021.10.001, doi:10.1016/bs.mie.2021.10.001. This article has 6 citations and is from a peer-reviewed journal.
12. (tsuji2021historicalrolesof pages 8-9): P. Tsuji, Didac Santesmasses, Byeong J. Lee, V. Gladyshev, and D. Hatfield. Historical roles of selenium and selenoproteins in health and development: the good, the bad and the ugly. International Journal of Molecular Sciences, Dec 2021. URL: https://doi.org/10.3390/ijms23010005, doi:10.3390/ijms23010005. This article has 50 citations and is from a peer-reviewed journal.