## Phylogeny

• Orthologs are present in Pseudomonas syringae (SelO), Escherichia coli (YdiU/MchC), Saccharomyces cerevisiae (Fmp40), Ostreococcus spp., Arabidopsis, most vertebrates including Homo sapiens and Mus musculus, while lost from nematodes and most insects (dudkiewicz2012anovelprotein pages 3-4).  
• Mammalian proteins retain a C-x-x-U motif; bacterial, fungal and plant homologs carry C-x-x-C at the equivalent position (tsuji2021historicalrolesof pages 8-9).  
• The catalytic core adopts a protein-kinase-like (PKL) fold; SelO defines an atypical pseudokinase family within the PKL superfamily (tomchick2019proteinampylationby pages 3-4).  
• Structural phylogeny clusters SelO with canonical bilobal kinases such as Csk1 and IRAK-4 despite divergent active-site chemistry (tomchick2019proteinampylationby pages 18-20).

## Reaction Catalyzed

ATP + protein-Ser/Thr/Tyr → protein-Ser/Thr/Tyr-AMP + PPi (tsuji2021historicalrolesof pages 8-9).

## Cofactor Requirements

Catalysis depends on divalent cations; Mg²⁺ and Ca²⁺ are coordinated in the active site of the 6EAC crystal structure (tomchick2019proteinampylationby pages 18-20).

## Substrate Specificity

• Accepts Ser, Thr and Tyr hydroxyl groups for AMPylation (tsuji2021historicalrolesof pages 8-9).  
• Consensus linear motif has not been defined; large-scale kinase substrate atlases have not reported SelO specificity (mukherjee2022identificationofselenoprotein pages 1-3).

## Structure

• Domain organisation: N-terminal mitochondrial targeting peptide; central kinase-like domain (~residues 120-470); C-terminal extension bearing the C-x-x-U redox motif (dudkiewicz2012anovelprotein pages 1-2, han2014characterizationofmammalian pages 1-2).  
• 2.27 Å crystal structure of P. syringae SelO (PDB 6EAC) shows a canonical N-lobe β-sheet and αC helix apposed to an α-helical C-lobe (tomchick2019proteinampylationby pages 18-20).  
• ATP binds in a flipped orientation, stabilised by an elongated glycine-rich loop and β8-αC insert unique to SelO (tomchick2019proteinampylationby pages 24-29).  
• Catalytic Asp262 coordinates metals; the conventional HRD base is absent, consistent with pseudokinase chemistry (tomchick2019proteinampylationby pages 18-20).  
• Modelled human SelO retains activation-loop, C-helix and hydrophobic spines typical of PKL kinases (dudkiewicz2012anovelprotein pages 6-8).

## Regulation

• Oxidative stress (H₂O₂) induces reversible formation of an 88 kDa mixed-disulfide/selenylsulfide complex via the C-x-x-U motif (han2014characterizationofmammalian pages 1-2).  
• Cys→Ser substitution in this motif abolishes complex formation, confirming redox control (dogaru2023“alphabet”selenoproteinstheir pages 3-4).  
• Intramolecular disulfide between Cys272 and Cys476 (E. coli numbering) modulates enzymatic activity; reduction by DTT re-activates the enzyme (tomchick2019proteinampylationby pages 4-6).  
• No phosphorylation or ubiquitination of SelO has been reported in the cited literature (tomchick2019proteinampylationby pages 4-6).  
• Selenocysteine incorporation is governed by a type 2 SECIS element; protein levels remain stable under dietary selenium deficiency (han2014characterizationofmammalian pages 6-7).

## Function

• Localises to mitochondria in mammalian and yeast cells (han2014characterizationofmammalian pages 1-2).  
• Maintains mitochondrial redox homeostasis; SelO knockout elevates GSH/GSSG and NADPH ratios (melo2024selenoproteinopromotes pages 9-10).  
• Regulates complex II activity and oxygen consumption; interaction partners include SdhA, Mdh2 and Idh2 (melo2024selenoproteinopromotes pages 9-10).  
• AMPylates glutaredoxin family proteins, influencing cellular S-glutathionylation under oxidative stress (tomchick2019proteinampylationby pages 8-9).  
• Broad tissue expression in mouse; expression priority is high during selenium limitation (han2014characterizationofmammalian pages 6-7).

## Other Comments

• Up-regulation of SELENOO promotes melanoma metastasis through modulation of mitochondrial metabolism (melo2024selenoproteinopromotes pages 9-10).  
• Variant rs5771225 (p.Val3Ala) associates with late-onset Alzheimer’s disease (santesmasses2021pathogenicvariantsin pages 9-11).  
• Missense mutations A263S and S262S reported in lung adenocarcinoma/squamous carcinoma cohorts (tian2023molecularmechanismsand pages 7-9).  
• Differential mRNA expression correlates with prognosis across multiple cancers, notably adverse in adrenocortical carcinoma and uveal melanoma (li2023apancancerstudy pages 2-5).

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