## Phylogeny

EIF2AK3/PERK is one of four members of the eIF2α-kinase (EIF2AK/eIF2K) family—together with HRI (EIF2AK1), PKR (EIF2AK2) and GCN2 (EIF2AK4)—within the CMGC group of the human kinome (Axten, 2017, pp. 1-7, 24-28). Functional orthologues have been described in mouse, Drosophila and C. elegans, underscoring strong evolutionary conservation of this ER-stress sensor (Donnelly et al., 2013, pp. 1-3).

## Reaction Catalyzed

ATP + [EIF2S1 protein] ⇌ ADP + [phospho-EIF2S1 protein] (Axten, 2017, pp. 1-7; Harding et al., 2012, pp. 1-2).

## Cofactor Requirements

Catalytic activity requires Mg²⁺ to coordinate ATP (Johnson et al., 2023, p. 4; Park, 2014, pp. 100-105).

## Substrate Specificity

• Principal target: EIF2S1/eIF2α Ser51 (Axten, 2017, pp. 15-19).  
• Peptide screens indicate a preference for proline immediately downstream of the phospho-acceptor site (Johnson et al., 2023, p. 4).  
• An alternative study reports better activity on arginine-rich sequences flanking the site (Park, 2014, pp. 100-105).

## Structure

Type I ER transmembrane protein with (i) N-terminal ER-luminal stress-sensing domain, (ii) single transmembrane helix, and (iii) C-terminal cytosolic kinase domain (Axten, 2017, pp. 1-7).  
• Luminal domain structure: PDB 4YZY.  
• Kinase-inhibitor complexes adopt a DFG-in active conformation (Park et al., 2024, pp. 13-16).  
• Key regulatory elements: activation loop, αC-helix, hydrophobic spine. Autophosphorylation on Thr980 stabilises the activation loop/αC-helix and is critical for activity (Donnelly et al., 2013, pp. 3-4).  
• Activated PERK forms back-to-back dimers that can linearly array to promote trans-autophosphorylation (Donnelly et al., 2013, pp. 3-4).

## Regulation

• ER stress releases BiP/GRP78 from the luminal domain, allowing PERK oligomerisation and trans-autophosphorylation (Axten, 2017, pp. 1-7; Donnelly et al., 2013, pp. 1-3).  
• Activating phosphorylation sites: Thr980 (activation loop) and Tyr615 (Donnelly et al., 2013, pp. 3-4).  
• Inhibitory phosphorylation: Tyr561 recruits Nck1, delaying activation (Unknown authors, 2015, pp. 105-112).  
• Negative feedback: ATF4-induced GADD34 (PPP1R15A) recruits PP1 to dephosphorylate eIF2α, attenuating signalling (Hicks et al., 2023, pp. 4-5, 11-13; English et al., 2022, pp. 2-4).

## Function

Major ER-stress sensor coupling the unfolded protein response (UPR) to the integrated stress response (ISR) (Axten, 2017, pp. 1-7).  
• Expression: high in secretory tissues, especially pancreatic β- and acinar cells (Axten, 2017, pp. 7-11).  
• Downstream effects: Ser51 phosphorylation of eIF2α globally represses cap-dependent translation while permitting selective translation of ATF4, which up-regulates CHOP, GADD34, ATF3 and TRB3 (Axten, 2017, pp. 1-11; Donnelly et al., 2013, pp. 1-3).  
• Additional substrates: NRF2 and GSK-3β (Unknown authors, 2015, pp. 39-43; Donnelly et al., 2013, pp. 3-4).  
• Physiological roles: pancreatic β-cell viability/insulin synthesis, skeletal development and post-natal growth (Zhang et al., 2002, p. 10; Unknown authors, 2014, pp. 9-15).  
• Outcome: transient activation is protective; chronic activation can drive apoptosis via ATF4/CHOP (Axten, 2017, pp. 11-15).

## Inhibitors

ATP-competitive small-molecule inhibitors include GSK2606414 and GSK2656157 (Axten, 2017, pp. 15-19, 24-28). Indoline amino-quinazoline derivatives represent an additional chemical series (Axten, 2017, pp. 19-24). PERK can be experimentally activated with the Fv2E-PERK fusion and the dimeriser AP20187 (Axten, 2017, pp. 11-15).

## Other Comments

Loss-of-function EIF2AK3 mutations cause Wolcott-Rallison Syndrome, characterised by early-onset insulin-dependent diabetes, skeletal defects and growth retardation; most pathogenic missense mutations map to the kinase domain (Axten, 2017, pp. 1-7; Park et al., 2024, pp. 9-13). Tauopathy-associated alleles cluster in the luminal domain, and the PERK-B haplotype confers heightened kinase activity and ER-stress sensitivity (Park et al., 2024, pp. 9-13; Ghura et al., 2024, pp. 1-2). Pancreatic toxicity observed with pharmacologic PERK inhibition phenocopies Wolcott-Rallison diabetes (Axten, 2017, pp. 15-19).

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