1. Phylogeny  
   EIF2AK3, commonly known as PERK (protein kinase RNA‐like endoplasmic reticulum kinase), is a serine/threonine protein kinase that belongs to the eIF2α kinase family. This family comprises several closely related stress‐sensing kinases including EIF2AK1 (HRI), EIF2AK2 (PKR) and EIF2AK4 (GCN2), and PERK is consistently found in metazoans, reflecting its fundamental role in the cellular response to endoplasmic reticulum (ER) stress (axten2013discoveryofgsk2656157 pages 4-5, cui2011thestructureof pages 1-2). Phylogenetic studies indicate that PERK is evolutionarily conserved across species, and its orthologs can be identified in organisms ranging from invertebrates to mammals. PERK forms part of an evolutionarily ancient set of kinases that mediate the integrated stress response (ISR) and unfolded protein response (UPR), a network that has been maintained from the last eukaryotic common ancestor (LECA) or earlier (marton2017asystemsbiological pages 1-3). Its conservation, together with other eIF2α kinases, underscores its critical role as a sensor that modulates translational control under adverse conditions (cui2011thestructureof pages 1-2).
2. Reaction Catalyzed  
   The primary biochemical reaction catalyzed by EIF2AK3/PERK is the transfer of a phosphate group from ATP to the hydroxyl group of a serine residue on its substrate. Specifically, PERK phosphorylates the alpha subunit of eukaryotic initiation factor 2 (eIF2α) at serine 51. In this reaction, ATP and eIF2α serve as substrates and the products are ADP and phosphorylated eIF2α, along with the release of a proton. This reaction is central to the ISR, as the phosphorylation of eIF2α results in a reduction of global protein synthesis while selectively permitting the translation of stress‐responsive mRNAs (axten2013discoveryofgsk2656157 pages 4-5, cui2011thestructureof pages 2-4).
3. Cofactor Requirements  
   The catalytic activity of PERK requires divalent cations as cofactors, with Mg²⁺ typically playing an essential role in facilitating its kinase function. As with most protein kinases, Mg²⁺ interacts with ATP to form a Mg²⁺–ATP complex, which is the actual substrate for the phosphorylation reaction. Although explicit experimental details in the provided context are limited, standard kinase biochemistry supports that Mg²⁺ is required for the optimal activity of PERK (stokes2022optimizationofa pages 18-20, cui2011thestructureof pages 5-6).
4. Substrate Specificity  
   EIF2AK3/PERK exhibits a high degree of substrate specificity for the alpha subunit of eukaryotic initiation factor 2 (eIF2α). PERK phosphorylates eIF2α at serine 51, a modification that is critical for mediating the translational repression observed during the unfolded protein response. There is no broad consensus motif beyond the requirement for the serine residue at this key regulatory position; rather, eIF2α is recognized by PERK as its primary and physiologically relevant substrate (axten2013discoveryofgsk2656157 pages 4-5, cui2011thestructureof pages 2-4).
5. Structure  
   EIF2AK3/PERK is a type I transmembrane protein composed of several distinct domains that underlie its dual roles in stress sensing and signal transduction. The N-terminal region is located in the endoplasmic reticulum lumen and functions as a stress-sensing domain. Under non-stress conditions, this luminal domain is bound by the chaperone BiP/GRP78, which maintains PERK in an inactive state. In response to ER stress caused by the accumulation of misfolded proteins, BiP dissociates and the luminal domain mediates dimerization and sometimes transient tetramerization of PERK, events that are crucial for its activation (cui2011thestructureof pages 4-5, carrara2015crystalstructuresreveal pages 9-10).

The single transmembrane segment anchors PERK to the ER membrane and connects the luminal stress-sensing region to the cytoplasmic portion. The C-terminal cytoplasmic domain contains the catalytic kinase domain, which is organized into a classical bilobal structure composed of an N-terminal lobe and a C-terminal lobe separated by a hinge region. Key structural features include the phosphate-binding P-loop, a well-defined activation loop that contains the critical autophosphorylation site threonine 980, and structural elements such as the C-helix that participate in forming the hydrophobic core necessary for catalytic activity (cui2011thestructureof pages 4-5, axten2013discoveryofgsk2656157 pages 4-5). Crystal structures and biochemical assays have revealed that, following dimerization, trans-autophosphorylation—particularly at Thr980—is essential for stabilizing the active conformation of the kinase domain. Additionally, specific residues within the kinase domain, such as those forming parts of the active site, contribute to the high selectivity of small-molecule inhibitors designed to target PERK (cui2011thestructureof pages 5-6, carrara2015crystalstructuresreveal pages 11-12).

1. Regulation  
   The regulation of PERK activity is tightly coupled to the protein folding status within the ER. Under basal conditions, PERK is maintained in an inactive state through its association with the chaperone BiP/GRP78. When misfolded or unfolded proteins accumulate, BiP is sequestered away from PERK, enabling its homodimerization and subsequent autophosphorylation at key residues such as Thr980, which is essential for full activation of the kinase (cui2011thestructureof pages 1-2, mounir2011aktdeterminescell pages 1-2).

In addition to stress-induced activation, PERK is subject to post-translational modification by other kinases. For example, Akt has been shown to negatively regulate PERK by phosphorylating it at threonine 799. This phosphorylation event by Akt impairs PERK’s ability to autophosphorylate at Thr980, thereby downregulating eIF2α phosphorylation and modulating cell fate decisions during stress (mounir2011aktdeterminescell pages 2-4, mounir2011aktdeterminescell pages 4-5). Thus, PERK activity is governed by a balance between activation via unfolded protein accumulation and inhibitory signals from other stress-related kinases. The reversible nature of PERK phosphorylation—and the subsequent dephosphorylation processes, mediated in part by phosphatase complexes such as those containing GADD34—ensures that its signaling is transient and can be attenuated once homeostasis is restored (mounir2011aktdeterminescell pages 7-8, mounir2011aktdeterminescell pages 8-10).

1. Function  
   EIF2AK3/PERK plays a central role in the unfolded protein response (UPR) and integrated stress response (ISR). Upon activation by ER stress, PERK phosphorylates eIF2α at serine 51, leading to a marked attenuation of global cap-dependent protein synthesis. This reduction in protein translation helps to alleviate the burden of newly synthesized proteins entering the stressed ER, thereby allowing the cell time to repair damaged proteins and restore normal function (axten2013discoveryofgsk2656157 pages 4-5, cui2011thestructureof pages 2-4).

Concomitantly, the phosphorylation of eIF2α leads to the preferential translation of specific mRNAs that contain upstream open reading frames (uORFs) in their 5′ untranslated regions. Notably, mRNAs encoding transcription factors such as ATF4 and QRICH1 are selectively translated under these conditions. Once synthesized, ATF4 transactivates a host of genes involved in amino acid metabolism, redox homeostasis, and protein folding, thereby reprogramming the cell’s gene expression profile to better cope with the stress (baird2014selectivemrnatranslation pages 1-2, axten2013discoveryofgsk2656157 pages 4-5).

PERK signaling is also implicated in the regulation of cell survival versus apoptosis. In cases of prolonged or overwhelming ER stress, the initially adaptive reductions in protein synthesis give way to the induction of pro-apoptotic signals mediated by factors such as CHOP. Thus, the functional output of PERK activation depends on the duration and severity of ER stress, with transient activation favoring cell survival and chronic activation often leading to apoptosis (mounir2011aktdeterminescell pages 5-7, smedley2021theroleof pages 1-2).

Beyond its canonical role in translational control during ER stress, PERK has been implicated in various physiological and pathological settings, including the regulation of pancreatic β-cell function, neurodegeneration (notably tauopathies such as Alzheimer’s disease and progressive supranuclear palsy), and cancer. In these contexts, PERK’s ability to modulate global protein synthesis and repair mechanisms positions it as a key mediator of cellular homeostasis under metabolic stress (park2023neurodegenerationriskfactor pages 1-2, perea2023perksignalingpromotes pages 1-2).

1. Other Comments  
   Several small-molecule inhibitors have been developed that target the kinase domain of PERK. For instance, compounds such as GSK2656157 and other optimized molecules from mandelamide-derived pyrrolopyrimidine series have demonstrated potent and selective inhibition of PERK activity in preclinical settings, with detailed structure–activity relationship studies guiding the optimization of such inhibitors (axten2013discoveryofgsk2656157 pages 4-5, stokes2022optimizationofa pages 1-2). Inhibitors that target PERK have been used to probe its function in cancer models and have revealed that pharmacological inhibition of PERK can reduce tumor growth by downregulating eIF2α phosphorylation and its downstream signaling cascades. However, the clinical translation of PERK inhibitors has been complicated by observations of pancreatic toxicity, which appears to be mediated in part by dysregulated type I interferon signaling and increased IFNAR1 stability in pancreatic tissues (yu2015typeiinterferons pages 1-3).

Genetic mutations in EIF2AK3 are causally linked to Wolcott–Rallison syndrome, a rare autosomal recessive disorder characterized by early-onset diabetes, exocrine pancreatic dysfunction, and skeletal dysplasia. In contrast, hypomorphic variants of PERK have been associated with an increased risk of neurodegenerative tauopathies, where impaired ER stress signaling contributes to the pathological aggregation of tau protein (park2023neurodegenerationriskfactor pages 2-3, smedley2021theroleof pages 7-9). Thus, PERK serves not only as a critical mediator of ER stress responses but also as a promising therapeutic target in diseases where ER homeostasis is perturbed.

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