## Phylogeny

EIF2AK2 (protein kinase R, PKR) is one of four eIF2α kinases (with HRI, PERK, GCN2) and is placed in the CMGC branch of the protein-kinase superfamily (Dar et al., 2005; Donnelly et al., 2013). It appears only in vertebrates and probably arose from a gene-duplication event of an ancestral eIF2α kinase such as GCN2/HRI (Rothenburg et al., 2016). A phylogenetic link between the C-lobe of its catalytic domain and the baculovirus protein PK2 suggests past horizontal gene transfer (Li et al., 2015).

## Reaction Catalyzed

ATP + [protein] ⇄ ADP + [phosphoprotein]  
Best-characterised reaction: ATP + eIF2α → ADP + phospho-eIF2α (Dar et al., 2005; Dey et al., 2014).

## Cofactor Requirements

Requires Mg²⁺ for ATP binding and phosphotransfer (Dar et al., 2005; Dey et al., 2014).

## Substrate Specificity

• Major substrate: eIF2α, Ser51 (Dar et al., 2005).  
• Efficient phosphorylation needs the intact eIF2α fold; Ser51 peptides alone are poor substrates, indicating extended docking contacts that include the kinase αG-helix (Dar et al., 2005; Taylor et al., 2005).  
• Positional-scanning peptide libraries define preferences at −5 to +5 around Ser/Thr (Johnson et al., 2023).  
• Primarily a Ser/Thr kinase but can also phosphorylate Tyr residues (Cesaro et al., 2021; Unknown Author, 2006).

## Structure

A 551-residue protein with two N-terminal dsRNA-binding motifs followed by a C-terminal kinase domain (residues 258–551) that exhibits the canonical bilobal fold (Dabo & Meurs, 2012).  
• Homodimerises “back-to-back” via N-lobes of the kinase (Unknown Author, 2006; Dey et al., 2014).  
• C-lobe houses the ATP site and an extended eIF2α docking surface formed by a distinctive αG-helix (Taylor et al., 2005).  
• Activation segment (432–458) contains the autophosphorylation site Thr446; phosphorylation here and coordination with helix αC stabilise the active state (Unknown Author, 2006; Dey et al., 2014).

## Regulation

• Trigger: binding of dsRNA ≥ 30–35 bp promotes dimerisation and cis-autophosphorylation on Thr446/Thr451 (Rothenburg et al., 2016; Dey et al., 2014).  
• Positive PTMs: ISGylation or SUMOylation at Lys60, 69, 150, 159, 440 produce constitutive activity (Bou-Nader et al., 2019).  
• Negative PTMs: phosphorylation of Ser6 and Ser97 dampens activity (Cesaro et al., 2021).  
• Protein partners: PACT/RAX activates; TRBP, ADAR1 and hDus2 inhibit; NF90 can act either way (Barber, 2005; Bou-Nader et al., 2019).

## Function

Interferon-inducible cytosolic/nuclear kinase that senses viral dsRNA, oxidative/ER stress and cytokines (Barber, 2005; Donnelly et al., 2013). Phosphorylation of eIF2α Ser51 converts eIF2α into an inhibitor of eIF2B, reducing global translation, promoting stress-granule formation and apoptosis, thereby limiting viral replication (Barber, 2005; Dabo & Meurs, 2012). Additional substrates include p53, and PKR serves as an adaptor in NF-κB, p38 MAPK and STAT pathways (Dabo & Meurs, 2012).

## Inhibitors

Viral RNAs (adenovirus VA, EBV EBER1/2) bind PKR and block activation; viral proteins NS1 (influenza), E3L and K3L (vaccinia) antagonise via dsRNA sequestration or eIF2α mimicry (Bou-Nader et al., 2019; Rothenburg et al., 2016; Dar et al., 2005). Cellular inhibitors include TRBP, hDus2 and ADAR1 (Bou-Nader et al., 2019).

## Other Comments

PKR dysregulation is associated with metabolic disease, cancer and neurodegeneration; phosphorylated PKR co-localises with Alzheimer’s aggregates (Bou-Nader et al., 2019; Dabo & Meurs, 2012). Loss-of-function mutation K296R abolishes catalytic activity; mutations that disrupt dimerisation or phosphomimetic Ser6/Ser97 substitutions also impair activation (Dey et al., 2014; Cesaro et al., 2021).

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