## Phylogeny

Orthologs of the enzyme occur in yeasts (Saccharomyces cerevisiae Ire1p; Schizosaccharomyces pombe Ire1), invertebrates (Caenorhabditis elegans IRE-1; Drosophila melanogaster Ire1), plants (Arabidopsis thaliana IRE1A/B) and all vertebrates (IRE1α/IRE1β) (Goupil et al., 2024). Vertebrates have two paralogs: the ubiquitously expressed IRE1α (ERN1) and the mucosa-restricted IRE1β (ERN2) (Goupil et al., 2024). The kinase domain belongs to the tyrosine-kinase-like (TKL) group, BCK1/IRE1 subfamily of the human kinome (Riaz et al., 2020).

## Reaction Catalyzed

ATP + [protein]-L-Ser/Thr ⇌ ADP + [protein]-O-phospho-L-Ser/Thr (Ferri et al., 2020).

## Cofactor Requirements

Mg²⁺ is required for phosphotransfer; Mn²⁺ can substitute in vitro (Mendez et al., 2015).

## Substrate Specificity

No strict Ser/Thr consensus motif has been defined. Cellular kinase substrates reported include BCL-2 (S70), FMRP, filamin A, pumilio (PUM1) and sphingosine-1-phosphate lyase (Goupil et al., 2024). The C-terminal RNase domain recognizes a CUGCAG stem-loop present in XBP1 mRNA and multiple RIDD targets (Goupil et al., 2024).

## Structure

Domain organisation: N-terminal ER-luminal sensor (S24–V390) → single-pass transmembrane helix → cytosolic Ser/Thr kinase (571–832) → C-terminal RNase (835–963) (Siwecka et al., 2021).  
Luminal domains dimerize via an MHC-like groove; higher-order oligomerization follows BiP release or direct peptide binding (Siwecka et al., 2021). Crystal studies show (i) face-to-face kinase dimers competent for trans-autophosphorylation (Ali et al., 2011) and (ii) back-to-back kinase dimers that juxtapose the RNase active sites for RNA cleavage (Ferri et al., 2020). Key catalytic motifs are VAIK, HRD and DFG (711-713); phosphorylation of S724/S726/S729 stabilises the active DFG-in/αC-in state (Ferri et al., 2020). The kinase front pocket is conformationally plastic, and ATP-competitive ligands can remodel it to allosterically modulate RNase activity (Ferri et al., 2020). The RNase catalytic Lys907 resides in a β-sheet-rich fold and can be covalently modified by salicylaldehyde inhibitors (Siwecka et al., 2021).

## Regulation

Post-translational modifications  
• Autophosphorylation on S724, S726 and S729 is required for full RNase activation (Ferri et al., 2020).  
• Additional phosphorylation at S840, S841, T844 and S850 fine-tunes signal amplitude (Read & Schröder, 2021).  
• Ubiquitination by MITOL/MARCHF5, CHIP, RNF13 and Synoviolin targets the protein for proteasomal degradation (Goupil et al., 2024).  
• Caspase-mediated cleavage of the cytosolic tail biases signalling toward apoptosis (Siwecka et al., 2021).

Allosteric and conformational control  
• BiP binding maintains an inactive monomer; BiP release allows luminal dimerization and cytosolic oligomerization (Siwecka et al., 2021).  
• Lipid bilayer stress or direct misfolded-protein binding can activate the enzyme independently of phosphorylation (Siwecka et al., 2021).  
• IRE1β can hetero-oligomerize with IRE1α to dampen RNase output in mucosal epithelia (Goupil et al., 2024).  
• Type I ligands (DFG-in) may paradoxically activate the RNase, whereas type II ligands (DFG-out) inhibit both kinase and RNase activities (Mendez et al., 2015).

## Function

IRE1α is expressed in virtually all tissues; IRE1β expression is limited to intestinal and airway epithelia (Goupil et al., 2024). As the principal ER-stress sensor, the RNase excises a 26-nt intron from XBP1 mRNA, yielding transcription factor XBP1s that induces chaperones and ERAD components (Ali et al., 2011). The enzyme also promotes regulated IRE1-dependent decay (RIDD) of selected ER-associated mRNAs to lower folding load (Ferri et al., 2020). Through TRAF2 recruitment it activates the ASK1-JNK and p38 MAPK cascades (Siwecka et al., 2021). Direct kinase substrates link ER stress to apoptosis (BCL-2), lipid metabolism (FMRP), cytoskeletal dynamics (filamin A), RNA stability (pumilio) and mitochondrial stress responses (SPL) (Goupil et al., 2024). IRE1 interacts with STIM1 and IP₃ receptors to influence ER-to-cytosol Ca²⁺ flux (Goupil et al., 2024). Sustained XBP1s signalling supports plasma-cell and pancreatic β-cell differentiation, and its overactivation favours survival of secretory cancers such as multiple myeloma (Ali et al., 2011).

## Inhibitors

Kinase-directed  
• Type I ATP-competitive: staurosporine, sunitinib (Ali et al., 2011); APY29 (Mendez et al., 2015).  
• Type II (DFG-out): KIRA6, KIRA7, KIRA8 (Siwecka et al., 2021).  
• Front-pocket modulator: G-1749 (Ferri et al., 2020).

RNase-directed  
• Salicylaldehydes (4µ8C) (Cross et al., 2012).  
• MKC-8866, MKC-3946, STF-083010, HNA (Siwecka et al., 2021).  
• Toyocamycin (Jiang et al., 2015).

Allosteric activators  
• Quercetin, ADP analogues (Jiang et al., 2015).  
• IXA1/4/6 (Siwecka et al., 2021).

## Other Comments

Aberrant IRE1 signalling is implicated in cancer, metabolic syndrome, inflammation and neurodegeneration (Riaz et al., 2020). No recurrent oncogenic point mutations have been firmly established (Goupil et al., 2024).

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