## Phylogeny

Mammals encode two paralogues, IRE1α (ERN1) and IRE1β (ERN2), that arose by gene duplication and share ~39 % overall sequence identity (Goupil et al., 2024). Orthologues include IRE1/IRE2 in Saccharomyces cerevisiae and the murine Irelpp gene (Goupil et al., 2024; Unknown authors, 2018). The kinase and RNase domains are strongly conserved across species, whereas the luminal stress-sensing domain is divergent (Goupil et al., 2024; Unknown authors, 2018). Within the human kinome, ERN2 is placed in the “Other” group (Zhou et al., 2021).

## Reaction Catalyzed

ATP + [a protein] ⇌ ADP + [a phosphoprotein] (Zhou et al., 2021).

## Cofactor Requirements

Catalysis requires ATP and a divalent cation, typically Mg²⁺ or Mn²⁺ (Prasad & Greber, 2021; Zhou et al., 2021; Riaz et al., 2020).

## Substrate Specificity

The RNase domain selectively cleaves 28S rRNA, thereby repressing translation (Goupil et al., 2024). Consensus motifs for the serine/threonine kinase activity have not been defined (Johnson et al., 2023 priority cited by Goupil et al., 2024).

## Structure

ERN2 is a type-I ER transmembrane protein comprising an N-terminal luminal domain (NLD), a single transmembrane segment, and a C-terminal cytosolic region that contains adjacent serine/threonine kinase and endoribonuclease domains (Prasad & Greber, 2021; Zhou et al., 2021). The NLD adopts a triangular β-sheet fold that promotes dimerization (Zhou et al., 2021). Amino-acid identity with human IRE1α is ~80 % in the kinase domain and ~61 % in the RNase domain (Riaz et al., 2020). Several non-conserved residues in the kinase active site underpin reduced catalytic efficiency (Goupil et al., 2024). Structural information on the activation loop and C-helix remains incomplete (Goupil et al., 2024).

## Regulation

Like other IRE1 proteins, activation entails oligomerization and trans-autophosphorylation (Prasad & Greber, 2021; Goupil et al., 2024). ERN2 is deficient in both phosphorylation and higher-order oligomer formation relative to IRE1α (Grey et al., 2020). It hetero-oligomerises with IRE1α and acts as a dominant-negative inhibitor of the latter’s RNase activity; this suppression is structural and does not depend on ERN2’s own kinase or RNase functions (Goupil et al., 2024; Grey et al., 2020). Specific post-translational modification sites on ERN2 have not been mapped (Goupil et al., 2024).

## Function

ERN2 is highly expressed in the mucosal epithelia of the gastrointestinal and respiratory tracts (Goupil et al., 2024; Prasad & Greber, 2021). By cleaving 28S rRNA, it provokes translational inhibition during ER stress (Goupil et al., 2024). Through hetero-association with IRE1α, ERN2 down-tunes canonical IRE1α signaling, thereby modulating the unfolded protein response (Goupil et al., 2024; Grey et al., 2020). Direct physical interaction with IRE1α has been demonstrated (Grey et al., 2020).

## Other Comments

IRE1 family members are linked to diverse pathologies, including diabetes, cancer and neurodegeneration, although ERN2-specific disease roles are not yet defined (Riaz et al., 2020). Unlike IRE1α knockout mice, ERN2 null mice are viable (Zhou et al., 2021). A kinase-dead IRE1α mutant phenocopies ERN2, showing impaired autophosphorylation and oligomerization (Grey et al., 2020).

## 9. References

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