## Phylogeny

IRAK2 is one of four mammalian interleukin-1 receptor-associated kinases (IRAK1, IRAK2, IRAK-M/IRAK3, IRAK4). Phylogenetic analyses indicate that the IRAK2 lineage arose from gene-duplication events of an ancestral IRAK4-like kinase early in vertebrate evolution (Gosu et al., 2012). Orthologs are conserved across mammals and invertebrates (e.g., the Drosophila Tube protein) (Benosman et al., 2013). IRAK2 is a non-RD serine/threonine kinase; its kinase and death-domain modules show high sequence conservation within the family, supporting a dual catalytic-scaffold role (Dardick & Ronald, 2006; Biswas & Tergaonkar, 2007).

## Reaction Catalyzed

ATP + L-seryl/threonyl-[protein] ⇌ ADP + H⁺ + O-phospho-L-seryl/threonyl-[protein] (Benosman et al., 2013).

## Cofactor Requirements

Mg²⁺ is required for ATP coordination and catalysis (Wang et al., 2006).

## Substrate Specificity

The exact consensus motif has not been conclusively defined. By analogy to related IRAKs, IRAK2 is thought to target serine/threonine residues positioned near basic amino acids (e.g., an RxRxxS/T-type context) in proteins that propagate NF-κB and stress-kinase signalling (Benosman et al., 2013; Gosu et al., 2012).

## Structure

IRAK2 is modular:  
• N-terminal death domain mediates homotypic binding to MyD88 and Myddosome assembly (Maschera et al., 1999; Benosman et al., 2013).  
• Central bilobal kinase domain contains the catalytic lysine, C-helix, activation segment, and lacks the typical RD motif, consistent with reduced intrinsic activity yet retained signalling function (Dardick & Ronald, 2006; Gosu et al., 2012).  
• C-terminal regions contribute to substrate recruitment and higher-order complex formation. Overall folding resembles IRAK4, supporting both enzymatic and scaffold functions (Gosu et al., 2012).

## Regulation

After IL-1/TLR engagement, IRAK2 is recruited to the receptor complex via its death domain and becomes part of the Myddosome with MyD88 and IRAK4. Upstream phosphorylation by IRAK4 promotes conformational activation (Benosman et al., 2013; Gosu et al., 2012). Alternative mRNA splicing produces isoforms with distinct capacities to propagate pro-inflammatory or ER-stress-induced apoptotic signals (Biswas & Tergaonkar, 2007; Smith et al., 2011). Spatial control is enforced through regulated Myddosome assembly (Benosman et al., 2013).

## Function

IRAK2 links IL-1 receptor and Toll-like receptor activation to downstream NF-κB, JNK and p38 MAPK pathways, promoting transcription of pro-inflammatory genes and stabilization of cytokine mRNAs (Benosman et al., 2013; Chaudhary et al., 2015). It also modulates endoplasmic-reticulum-stress responses by influencing CHOP-mediated apoptosis (Benosman et al., 2013). IRAK2 expression in innate immune cells is essential for robust cytokine production, and genetic variants affect IL-17 output during Th17 responses (Smith et al., 2011).

## Inhibitors

Selective chemical inhibitors for IRAK2 are not yet established; ongoing programmes aim to modulate IRAK family members to treat pathological inflammation (Winkler et al., 2021; Patra & Choi, 2016).

## Other Comments

IRAK2 knockdown or genetic deletion diminishes ER-stress-induced CHOP expression and alters apoptotic outcomes. Mouse strain-specific isoforms correlate with differential IL-1-induced IL-17 production, highlighting potential roles in autoimmune pathogenesis and therapeutic targeting (Benosman et al., 2013; Smith et al., 2011).

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