## Phylogeny

* Member of the tyrosine-kinase-like (TKL) group within the human kinome and one of four vertebrate IRAK paralogs (chaudhary2015recentadvancesin pages 3-4).
* Orthologs documented in Homo sapiens (IRAK4), Mus musculus (Irak4), and Drosophila melanogaster (Pelle), illustrating conservation from insects to mammals (wang2009irak4inhibitorsfor pages 1-2, chaudhary2015recentadvancesin pages 1-2).
* Multiple-sequence alignment across additional vertebrate species confirms broad evolutionary conservation of the kinase domain (dossang2016thenterminalloop pages 10-11).
* Kinase-family classification derived from large-scale kinome analyses supports placement of IRAK4 in the IRAK subfamily of the TKL group (wang2017crystalstructureof pages 6-6).

## Reaction Catalyzed

Protein-Ser/Thr + ATP ⇌ Protein-Ser/Thr-phosphate + ADP + H⁺ (patra2016recentprogressin pages 10-12, dossang2016thenterminalloop pages 10-11).

## Cofactor Requirements

Catalysis is ATP-dependent and requires divalent cations, with Mg²⁺ or Mn²⁺ supporting phosphoryl transfer (wang2019conformationalflexibilityand pages 8-10, dossang2016thenterminalloop pages 10-11).

## Substrate Specificity

* Immediate physiological substrates are IRAK1, IRAK2 and IRAK-M recruited within the Myddosome; a linear consensus motif has not been conclusively defined (chaudhary2015recentadvancesin pages 1-2).

## Structure

* Domain architecture: N-terminal death domain mediating MyD88 binding, Pro/Ser/Thr-rich linker, and a C-terminal bilobal kinase domain lacking the TRAF6-recruiting extension present in other IRAKs (chaudhary2015recentadvancesin pages 1-2, patra2016recentprogressin pages 1-3).
* Myddosome DD stack resolved at 3.7 Å with 6 MyD88 : 4 IRAK4 : 4 IRAK2 stoichiometry (PDB 3MOP) (chaudhary2015recentadvancesin pages 1-2).
* Kinase-domain structures determined in apo and inhibitor-bound forms (e.g., PDB 2NRU, 4U99) reveal a distinctive front pocket and a back pocket occluded by tyrosine gatekeeper Tyr262 (wang2009irak4inhibitorsfor pages 3-4, wang2019conformationalflexibilityand pages 1-2).
* Catalytic Lys213, hinge Met265 and gatekeeper Tyr262 form the core of the ATP site; π-stacking with Tyr262 underlies inhibitor selectivity over IRAK1 (genung2017smallmoleculeinhibition pages 5-8).
* Activation loop residues Thr342, Thr345, Ser346 and Thr352 undergo trans-autophosphorylation, stabilising the DFG-in/αC-in active state (patra2016recentprogressin pages 3-6).
* Unphosphorylated kinase alternates between active and inactive (DFG-out, αC-out) conformations that are trapped by type II inhibitors (wang2019conformationalflexibilityand pages 1-2).
* Homodimerisation through αEF/αG promotes trans-autophosphorylation; the phosphorylated kinase subsequently heterodimerises with IRAK1 (wang2017crystalstructureof pages 4-5).

## Regulation

* Autophosphorylation at Thr342, Thr345, Ser346 and Thr352 is obligatory for catalytic activation (patra2016recentprogressin pages 3-6).
* Phosphate coordination by Arg310, Arg334 and Arg347 mimics tyrosine-kinase activation-loop contacts (wang2009irak4inhibitorsfor pages 3-4).
* Ordered assembly into the Myddosome (6 MyD88 : 4 IRAK4 : 4 IRAK2) positions IRAK4 for activation; the N-terminal loop of the death domain fine-tunes assembly kinetics (chaudhary2015recentadvancesin pages 1-2, dossang2016thenterminalloop pages 10-11).
* Conformational control: unphosphorylated kinase homodimerises for activation, whereas the phosphorylated enzyme forms transient heterodimers with IRAK1 to propagate signalling (wang2017crystalstructureof pages 1-1).

## Function

* Broadly expressed, with prominent roles in hematopoietic and immune tissues where it acts as the apical kinase in MyD88-dependent Toll-like receptor and IL-1 receptor signalling (patra2016recentprogressin pages 8-10).
* Upstream input: ligand-occupied TLRs/IL-1R recruit MyD88, which directly engages IRAK4 via death-domain interactions (chaudhary2015recentadvancesin pages 1-2).
* Downstream events: IRAK4 phosphorylates IRAK1/2, enabling TRAF6 recruitment, TAK1 activation, and subsequent NF-κB, JNK and p38 MAPK cascades; it is additionally required for TLR7/9-mediated IRF5/7 activation and type I interferon production (wang2009irak4inhibitorsfor pages 2-3, chaudhary2015recentadvancesin pages 1-2).
* Participates in NLRP3 inflammasome priming within macrophages (patra2016recentprogressin pages 8-10).

## Inhibitors

* Natural product reference: staurosporine – type I ATP-competitive probe (wang2009irak4inhibitorsfor pages 3-4).
* Selective clinical/pre-clinical small molecules:  
  • PF-06650833, orally bioavailable, whole-blood potent inhibitor (genung2017smallmoleculeinhibition pages 38-41).  
  • Takeda pyrazolo-diamines (compounds 80/81), complete enzymatic inhibition at 1 µM and in-vivo anti-inflammatory efficacy (genung2017smallmoleculeinhibition pages 38-41).  
  • 9-Cyano-indolo[2,3-c]quinolones, IC₅₀ ≈ 7 nM, hinge Met265 H-bond and Tyr262 π-stacking (patra2016recentprogressin pages 8-10).  
  • Type I inhibitors JH-I-25 and JH-I-17 bound to active conformation (wang2019conformationalflexibilityand pages 16-18).  
  • Type II inhibitors ponatinib and HG-12-6 stabilising DFG-out inactive state (wang2019conformationalflexibilityand pages 16-18).  
  • ND-2158 and BAY 1830839 under evaluation for B-cell malignancies and inflammation (rhyasen2015iraksignallingin pages 5-5).
* Synergy reported with BTK, SYK and PI3Kδ inhibitors in MYD88-mutant lymphomas (chaudhary2015recentadvancesin pages 3-4).

## Other Comments

* Autosomal recessive IRAK4 deficiency (OMIM 607676) causes susceptibility to recurrent pyogenic bacterial infections due to impaired TLR/IL-1R signalling (wang2009irak4inhibitorsfor pages 12-12).
* Kinase-dead knock-in mice exhibit defective cytokine production and resistance to septic shock, validating catalytic activity as essential in vivo (chaudhary2015recentadvancesin pages 1-2).
* MYD88 L265P gain-of-function mutations in ABC-DLBCL and Waldenström macroglobulinemia create oncogenic dependence on IRAK4; selective inhibitors suppress proliferation and enhance efficacy of B-cell receptor pathway drugs (chaudhary2015recentadvancesin pages 3-4, rhyasen2015iraksignallingin pages 5-5).
* Aberrant IRAK4 signalling contributes to rheumatoid arthritis, systemic lupus erythematosus and psoriasis, highlighting broad therapeutic potential (patra2016recentprogressin pages 3-6).

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