## Phylogeny

The interleukin-1 receptor-associated kinase (IRAK) family comprises IRAK1, IRAK2, IRAK3 (IRAK-M) and IRAK4, a subgroup of the TKL (Tyrosine-kinase-like) branch of the human kinome (Janssens & Beyaert, 2003; Mahmoud et al., 2023). The family is evolutionarily related to Drosophila Pelle, and an IRAK4-like gene is viewed as the ancestral form from which the other IRAKs diverged (Freihat, 2017). IRAK proteins are highly conserved across vertebrates (Pereira & Gazzinelli, 2023). Human IRAK3 is a class I pseudokinase, whereas the rodent orthologue retains a catalytic asparagine that may confer kinase activity (Freihat, 2017).

## Reaction Catalyzed

No ATP-dependent phosphotransferase reaction has been detected; human IRAK3 is catalytically inactive as a protein kinase (Freihat, 2017; Lange et al., 2021).

## Cofactor Requirements

The pseudokinase domain does not efficiently bind Mg²⁺/Mn²⁺ required for kinase activity (Freihat, 2017). A predicted guanylate-cyclase centre is expected to use Mn²⁺ coordinated by D377 and D385 (Turek et al., 2023).

## Substrate Specificity

Human IRAK3 shows little or no phosphorylation activity and therefore no kinase substrate motif has been defined (Freihat, 2017; Suzuki et al., 2005). The only confirmed substrate for its embedded guanylate-cyclase module is GTP (Freihat, 2017; Turek et al., 2023).

## Structure

IRAK3 contains an N-terminal death domain, a proline/serine/threonine-rich region, a central pseudokinase domain and a C-terminal tail (Lange et al., 2021; Flannery & Bowie, 2010).  
• The pseudokinase adopts a canonical kinase fold in a closed, pseudo-active conformation with an atypical Ser293 in the HRD motif and a DFA in place of DFG (Lange et al., 2021; Freihat, 2017).  
• The activation loop adopts the BLAminus configuration and the hydrophobic spine is characteristic of an inactive state (Lange et al., 2021).  
• A unique head-to-head dimer is formed through a redox-sensitive disulphide between C291 (catalytic loop) and C202 (αC helix) of opposite protomers (Lange et al., 2021; Horne & Murphy, 2021).  
• The guanylate-cyclase catalytic centre resides within the pseudokinase C-lobe (Freihat, 2017).

## Regulation

IRAK3 lacks autophosphorylation (Freihat, 2017) but is controlled allosterically through its redox-sensitive dimer interface, which may tune negative regulation of IRAK4 (Lange et al., 2021). IRAK family members are subject to ubiquitination by E3 ligases such as TRAF6 and Pellino proteins, although direct evidence for IRAK3 ubiquitination is limited in the current context (Pereira & Gazzinelli, 2023; Horne & Murphy, 2021).

## Function

Predominantly expressed in monocytes, macrophages, dendritic cells and airway epithelial cells (Freihat, 2017; Mahmoud et al., 2023). IRAK3 integrates into the MyD88-dependent myddosome and negatively modulates Toll-like receptor (TLR) and IL-1 receptor signalling (Freihat, 2017; Turek et al., 2023).  
• Interacts with MyD88 and other IRAKs; reports differ on whether it binds IRAK1, IRAK2 or both (Freihat, 2017).  
• Restricts NF-κB and MAPK pathway activation, lowering pro-inflammatory cytokine production (Freihat, 2017; Turek et al., 2023).  
• cGMP generated by its guanylate-cyclase activity further suppresses NF-κB signalling (Turek et al., 2023).  
• At low TLR ligand doses, preferential recruitment of IRAK3 leads to induction of inhibitory mediators (SOCS1, SHIP1, A20) (Freihat, 2017).

## Inhibitors

Although catalytically inactive, IRAK3 retains an intact ATP-binding cleft and can bind ATP-competitive small molecules, probably with low affinity; no specific inhibitors have yet been described (Freihat, 2017; Patra & Choi, 2016; Singer et al., 2018).

## Other Comments

IRAK3 dysregulation is linked to autoimmune and inflammatory disorders. High expression correlates with immunosuppression and poor outcomes in sepsis and pneumococcal lung injury (Freihat, 2017). Asthma-associated mutations cluster on a conserved surface implicated in IRAK4 interaction (Lange et al., 2021). Death-domain mutants (E71A, Q78G, W74A) disrupt IRAK4 binding, while mutations near the guanylate-cyclase centre (e.g., D377 or D385) alter localisation and immunomodulatory capacity (Freihat, 2017; Turek et al., 2023).

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