## Phylogeny

IRAK3 (also called IRAK-M) is a member of the interleukin-1 receptor-associated kinase family (IRAK-1, IRAK-2, IRAK-3, IRAK-4). It is conserved across vertebrates that possess sophisticated innate immune systems and shares the canonical IRAK domain architecture of an N-terminal death domain followed by a central (pseudo)kinase fold (Janssens & Beyaert, 2003; Flannery & Bowie, 2010). Unlike the catalytically competent IRAK-1 and IRAK-4, IRAK3 accumulated substitutions at key catalytic residues, evolving into a pseudokinase that functions primarily as a negative modulator of IL-1R/TLR signalling (Janssens & Beyaert, 2003; Flannery & Bowie, 2010).

## Reaction Catalyzed

Protein serine/threonine kinases normally mediate:  
ATP + [protein]-L-Ser/Thr ⇌ ADP + H⁺ + [protein]-O-phospho-L-Ser/Thr

IRAK3 lacks the catalytic aspartate in the DFG motif and does not catalyse this reaction (Jain et al., 2014; Janssens & Beyaert, 2003; Bahia et al., 2015).

## Cofactor Requirements

Active serine/threonine kinases require Mg²⁺ to coordinate ATP, yet no Mg²⁺-dependent catalytic activity has been demonstrated for IRAK3 (Flannery & Bowie, 2010; Lange et al., 2021).

## Substrate Specificity

Because IRAK3 is enzymatically inert, no consensus phosphorylation motif or substrate preference has been defined (Jain et al., 2014; Bahia et al., 2015).

## Structure

IRAK3 comprises an N-terminal death domain that recruits the protein to MyD88-containing receptor complexes and a central pseudokinase domain that retains the bilobed kinase fold but adopts a “closed” pseudoactive conformation (Lange et al., 2021). The G-loop is rigidified by hydrophobic interactions around a conserved phenylalanine, and the ATP-binding pocket retains an invariant lysine (e.g., K192) but contains a DFA (not DFG) motif and altered catalytic loop residues that prevent phosphotransfer (Flannery & Bowie, 2010). Crystal structures reveal head-to-head dimerisation mediated by αC-helix interactions, proposed to stabilise an autoinhibited state (Lange et al., 2021). Dimer formation may also be influenced by redox-regulated disulphide bridges (Horne & Murphy, 2021).

## Regulation

IRAK3 negatively regulates IL-1R and Toll-like receptor signalling by preventing the dissociation and subsequent phosphorylation of IRAK-1 and IRAK-4 within the MyD88 complex, thereby dampening NF-κB activation (Flannery & Bowie, 2010). It selectively blocks the alternative NF-κB pathway (Su et al., 2009) yet can promote expression of specific cytokine mRNAs (IL6, CSF3, CXCL2, CCL5) in IL-33-stimulated dendritic cells (Zhou et al., 2013). Regulation is driven largely by protein–protein interactions, dimerisation, and inducible expression rather than by phosphorylation or ubiquitination (Horne & Murphy, 2021; Su et al., 2009). Expression is highest in monocytes, macrophages, and dendritic cells and is inducible during inflammatory responses (Mahmoud et al., 2023; Ringwood & Li, 2008).

## Function

Predominantly expressed in myeloid lineage cells, IRAK3 limits excessive inflammatory signalling, contributes to endotoxin tolerance, and protects against pathological inflammation such as sepsis and chronic inflammatory disease (Flannery & Bowie, 2010; Rhyasen & Starczynowski, 2015; Ringwood & Li, 2008). Context-dependent positive roles have been noted, e.g., enhanced cytokine transcription during IL-33-mediated lung inflammation (Tunalı et al., 2023). By fine-tuning TLR/IL-1R pathways, IRAK3 maintains immune homeostasis.

## Inhibitors

IRAK3 lacks catalytic activity; therefore, classical ATP-competitive kinase inhibitors are ineffective. Nonetheless, its scaffold function is being explored as an immune checkpoint target: genetic deletion or blockade in myeloid cells augments anti-tumour immunity (Tunalı et al., 2023). PROTACs or protein–protein interaction disruptors have been proposed, but no direct inhibitors are yet reported (Wiese et al., 2020; Tunalı et al., 2023).

## Other Comments

Polymorphisms in IRAK3 predict responsiveness to anti-TNF therapy in rheumatoid arthritis, highlighting clinical relevance (Wiese et al., 2020). Although not drugged directly, the protein’s regulatory role in cytokine storms (e.g., SARS-CoV-2 infection) makes it an attractive therapeutic target (Mahmoud et al., 2023).

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