## Proposed EC/sub-subclass

2.7.11.– (protein-serine/threonine kinases)

## Accepted name

Interleukin-1 receptor-associated kinase 1

## Synonyms

IRAK1; Pelle-like kinase; Interleukin-1 receptor-associated kinase-1; IL-1R-associated kinase-1

## Phylogeny

IRAK1 is a conserved serine/threonine kinase found throughout mammals and evolutionarily related to the other IRAK paralogues (IRAK4, IRAK2 and the pseudokinase IRAK-M). Homology with the Drosophila Pelle kinase indicates that the gene duplication events producing the present IRAK family pre-date the vertebrate lineage, highlighting an ancient, conserved role in Toll-like receptor (TLR) and interleukin-1 receptor (IL-1R) signalling (Gosu et al., 2012; Janssens & Beyaert, 2003; Gottipati et al., 2008).

## Reaction catalysed

ATP + L-seryl/threonyl-[protein] ⇌ ADP + H⁺ + O-phospho-L-seryl/threonyl-[protein] (Flannery & Bowie, 2010; Jain et al., 2014)

## Cofactor requirements

Mg²⁺ is required for efficient ATP binding and catalysis (Flannery & Bowie, 2010; Wang et al., 2017).

## Substrate specificity

IRAK1 phosphorylates serine/threonine residues within several signalling proteins, although a strict consensus motif has not been defined. Confirmed cellular substrates include Pellino family E3 ligases (PELI1-3), the adaptor TIRAP/MAL, interferon-regulatory factor 7 (IRF7) and, after SUMO modification and nuclear translocation, STAT3. These phosphorylation events promote downstream polyubiquitination, adaptor turnover or transcription-factor activation in TLR/IL-1R pathways (Gottipati et al., 2008; Flannery & Bowie, 2010; Jain et al., 2014).

## Structure

Full-length IRAK1 comprises  
• N-terminal death domain that docks to MyD88;  
• Proline/Ser/Thr-rich (ProST) segment involved in autophosphorylation and ubiquitin-dependent turnover;  
• Central bilobal kinase domain with catalytic Lys239, gatekeeper Tyr288 and catalytic Asp340;  
• Activation-loop residues Thr209 and Thr387 that are phosphorylated first by IRAK4 then by IRAK1 itself to achieve full activity.

Crystal structures of the isolated kinase domain reveal a canonical protein-kinase fold and a Tyr gatekeeper that defines the ATP-pocket architecture unique to the IRAK family. Biochemical and structural analyses suggest autoinhibition in the full-length protein that is relieved upon activation-loop phosphorylation (Wang et al., 2017; Flannery & Bowie, 2010; Jain et al., 2014).

## Regulation

• Upstream activation: IRAK4 phosphorylates Thr209/Thr387 after receptor engagement, triggering IRAK1 autophosphorylation and dissociation from the MyD88 “myddosome” (Gottipati et al., 2008; Flannery & Bowie, 2010).  
• Ubiquitination: Pellino-dependent polyubiquitination recruits TAK1 and the IKK complex via NEMO, propagating NF-κB activation; PEST motifs foster proteasomal degradation for negative feedback (Suzuki et al., 2005; Flannery & Bowie, 2010).  
• Sumoylation: promotes nuclear import where IRAK1 phosphorylates STAT3 and modulates IL-10 and interferon responses (Li, 2005; Singer et al., 2018).  
• Alternative splicing: the kinase-inactive variant IRAK1b can still participate in signalling complexes and modulate NF-κB output (Jensen & Whitehead, 2001; Gottipati et al., 2008).

## Function

Broadly expressed in monocytes, macrophages, dendritic cells, T and B lymphocytes, IRAK1 is a pivotal kinase in innate immunity. Following TLR or IL-1R stimulation, IRAK1 phosphorylates:  
– Pellino E3 ligases to enable K63-linked polyubiquitination and assembly of the IRAK1–TRAF6–TAK1 complex leading to NF-κB activation;  
– TIRAP to tag it for ubiquitin-mediated degradation, curbing signal duration;  
– IRF7 to drive type I interferon gene transcription in antiviral responses;  
– STAT3 (after SUMO-mediated nuclear translocation) to modulate anti-inflammatory cytokine production (Flannery & Bowie, 2010; Singer et al., 2018).

## Inhibitors

Pacritinib, developed as a JAK2/FLT3 inhibitor, potently inhibits IRAK1 and suppresses pro-inflammatory cytokine production. Additional small-molecule ATP-competitive inhibitors exploit the unique Tyr gatekeeper to achieve selectivity and are being explored for inflammatory disorders and malignancies (Singer et al., 2018; Rhyasen & Starczynowski, 2015; Bahia et al., 2015).

## Other Comments

Aberrant IRAK1 activity is implicated in autoimmune diseases (e.g., systemic lupus erythematosus, rheumatoid arthritis), chronic inflammatory conditions and several cancers. Splice variants such as IRAK1b add complexity to disease-related signalling phenotypes (Flannery & Bowie, 2010; Singer et al., 2018; Gottipati et al., 2008).

## References

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