1. Phylogeny  
   IRAK3 belongs to the interleukin‐1 receptor‑associated kinase (IRAK) family, a group of proteins that also includes IRAK‐1, IRAK‐2, and IRAK‑4. Unlike its catalytically active counterparts, IRAK3 has evolved into a pseudokinase with specialized regulatory functions. This protein is conserved among vertebrates and is predominantly present in species that possess sophisticated innate immune systems. Within the context of the human kinome, IRAK3 is grouped with other IRAK family members that share a common domain organization, including an N‑terminal death domain and a centrally located kinase (or pseudokinase) domain. Phylogenetic analyses suggest that while IRAK‑1 and IRAK‑4 have retained catalytic activity necessary for signal propagation downstream of IL‑1 receptor family members and Toll‑like receptors (TLRs), IRAK3 diverged by acquiring key amino acid substitutions at its catalytic residues, a modification that established its role as a negative modulator of inflammation (janssens2003functionaldiversityand pages 2-3, flannery2010theinterleukin1receptorassociated pages 1-5).
2. Reaction Catalyzed  
   As a member of the protein kinase family, active kinases usually catalyze the transfer of a phosphate group from ATP to a serine or threonine residue on a substrate protein, following the reaction: ATP + [protein]‑(L‑serine or L‑threonine) → ADP + [protein]‑(L‑serine/threonine)‑phosphate + H⁺. However, IRAK3 is a pseudokinase due to substitutions in its catalytic motifs, including the absence of the critical catalytic aspartate residue in the conserved DFG motif; as a result, it does not perform classical phosphorylation reactions (jain2014il1receptorassociatedkinase pages 2-3, janssens2003functionaldiversityand pages 2-3, bahia2015interleukin1receptorassociated pages 3-4).
3. Cofactor Requirements  
   In catalytically active serine/threonine kinases, the presence of divalent cations such as Mg²⁺ is typically essential to facilitate ATP binding and phosphoryl transfer. While IRAK3 retains an ATP-binding pocket that features an invariant lysine residue important for nucleotide binding, it does not exhibit kinase activity; thus, although its structure is consistent with that of Mg²⁺‑dependent kinases, no cofactor-dependent catalytic activity has been demonstrated for IRAK3 (flannery2010theinterleukin1receptorassociated pages 43-47, lange2021dimericstructureof pages 3-4).
4. Substrate Specificity  
   For active kinases, substrate specificity is often dictated by recognition of consensus motifs, such as the RxRxxp[S/T] motif observed in many serine/threonine kinases. In contrast, IRAK3 lacks the catalytic functionality required to phosphorylate substrates. Because the protein is enzymatically inactive, no specific consensus substrate motifs or phosphorylation preferences have been defined for IRAK3 (jain2014il1receptorassociatedkinase pages 2-3, bahia2015interleukin1receptorassociated pages 3-4).
5. Structure  
   IRAK3 is organized into several domains reminiscent of its catalytically active IRAK family members. It contains an N‑terminal death domain (DD) that mediates protein–protein interactions essential for its recruitment to receptor complexes such as the MyD88 complex, followed by a central pseudokinase domain that, despite retaining the overall bilobed kinase fold, harbors key amino acid substitutions responsible for its lack of catalytic activity. Structural studies have revealed that the pseudokinase domain of IRAK3 adopts a “closed”, pseudoactive conformation in which the αC‑helix is oriented inward, and the regulatory hydrophobic spine is partially assembled. Notably, the G‑loop is uniquely stabilized by hydrophobic interactions—centered around a conserved phenylalanine residue—resulting in a rigid conformation even in the absence of ATP (lange2021dimericstructureof pages 1-3, lange2021dimericstructureof pages 5-6). Furthermore, IRAK3 forms a head‑to‑head dimer through interactions mediated by its pseudokinase domain, including contacts involving the αC‑helix and additional interface residues; such dimerization is proposed to facilitate its allosteric inhibitory role by stabilizing a conformation incompatible with substrate phosphorylation (lange2021dimericstructureof pages 1-3, lange2021dimericstructureof pages 3-4). Although an invariant lysine residue (for example, K192) is maintained within the ATP binding pocket, other features important for kinase activity—such as a modified DFG motif (often observed as DFA) and alterations in the catalytic loop—emphasize its divergence from active kinases (flannery2010theinterleukin1receptorassociated pages 43-47, li2005il1receptor–associatedkinase pages 1-2).
6. Regulation  
   IRAK3 functions as a key negative regulator in the IL‑1R and TLR signaling cascades by modulating the assembly and disassembly of the receptor complex. Its primary regulatory mechanism involves inhibition of the dissociation of IRAK1 and IRAK4 from the MyD88 receptor complex, a process that normally leads to downstream activation of NF‑κB. By stabilizing this complex, IRAK3 prevents the necessary phosphorylation events on IRAK1 and IRAK4, thereby dampening the propagation of the pro‑inflammatory signal (flannery2010theinterleukin1receptorassociated pages 16-20, flannery2010theinterleukin1receptorassociated pages 20-24). In addition, studies indicate that IRAK3 can selectively inhibit the alternative NF‑κB pathway while allowing limited or altered activation of NF‑κB transcriptional programs; for instance, under certain conditions such as IL‑33–induced lung inflammation, IRAK3 positively regulates the expression of specific mRNAs, including IL6, CSF3, CXCL2, and CCL5 in dendritic cells (zho2013irak‐mmediatestoll‐like pages 1-2). Post‑translational modifications that typically regulate kinase activity, such as phosphorylation or ubiquitination, have not been delineated as major regulatory events for IRAK3; instead, its regulation is largely mediated by protein–protein interactions and conformational rearrangements, including dimerization that may be influenced by redox status through disulfide bridge formation (horne2021forwhomthe pages 2-2, su2009theinterleukin1receptorassociated pages 8-9, su2009theinterleukin1receptorassociated pages 9-10). Expression of IRAK3 is also tightly controlled, with inducible expression being predominantly restricted to monocytes, macrophages, and dendritic cells, which further underscores its specialized role in modulating innate immune responses (mahmoud2023modulationofirak pages 4-6, ringwood2008theinvolvementof pages 5-6).
7. Function  
   IRAK3 plays a central role in the regulation of innate immune signaling by functioning as an inhibitory modulator that prevents excessive inflammatory responses. It is predominantly expressed in cells of the myeloid lineage such as monocytes, macrophages, and dendritic cells. Functionally, IRAK3 inhibits the dissociation of IRAK1 and IRAK4 from the MyD88 receptor complex following stimulation by Toll‑like receptors or the interleukin‑1 receptor, which in turn prevents the full activation of NF‑κB and subsequent transcription of pro‑inflammatory cytokines. This inhibitory action contributes to the phenomena of endotoxin tolerance, wherein repeated exposure to TLR ligands results in hyporesponsiveness. In certain contexts, such as during IL‑33–induced inflammation in the lung, IRAK3 has also been reported to positively influence the expression of cytokine and chemokine mRNAs (IL6, CSF3, CXCL2, and CCL5) in dendritic cells, indicating that its role may differ according to the cellular context and nature of the stimulus (flannery2010theinterleukin1receptorassociated pages 16-20, flannery2010theinterleukin1receptorassociated pages 20-24, tunalı2023il1receptor–associatedkinase3 pages 7-9). Moreover, by controlling the amplitude and duration of TLR/IL‑1R signaling, IRAK3 contributes to the maintenance of immune homeostasis and prevents pathological inflammatory conditions such as sepsis and chronic inflammatory diseases (rhyasen2015iraksignallingin pages 2-3, ringwood2008theinvolvementof pages 10-13).
8. Other Comments  
   Given its pseudokinase nature, IRAK3 is not a target for inhibition via classical kinase inhibitors aimed at blocking catalytic activity. However, its biological role as an immune checkpoint has garnered interest in the context of cancer immunotherapy, where its deletion or blockade in myeloid cells has been associated with enhanced antitumor immunity (tunalı2023il1receptor–associatedkinase3 pages 7-9). Additionally, polymorphisms in the IRAK3 gene have been identified as predictive genetic markers for responsiveness to anti‑TNF therapy in rheumatoid arthritis, underscoring its clinical relevance in autoimmune diseases (wiese2020investigationalirak4inhibitors pages 17-21). Although no specific inhibitors that directly target the scaffolding or regulatory functions of IRAK3 have been reported, its involvement in modulating signaling complexes makes it an attractive candidate for therapeutic intervention by new modalities such as protein–protein interaction disruptors or PROTACs (tunalı2023il1receptor–associatedkinase3 pages 7-9, wiese2020investigationalirak4inhibitors pages 17-21).
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