1. Phylogeny  
   IRAK2 (Interleukin-1 receptor-associated kinase-like 2) belongs to the IRAK family of kinases, a group that is conserved throughout metazoans and can be traced back to the common ancestor of animals. Within the human kinome, IRAK2 is grouped alongside IRAK1, IRAK4, and IRAK-M, and its presence in mammals is supported by its identification in multiple species. Comparative sequence analyses reveal that IRAK2, like other family members, possesses a conserved N-terminal death domain as well as a central kinase domain, although its catalytic capacity has been a matter of debate in the literature. Phylogenetic studies have placed IRAK2 in close evolutionary proximity to IRAK1, with divergence likely occurring during early vertebrate evolution, as illustrated by molecular evolutionary analyses that compare vertebrate IRAKs with insect homologs such as Pelle and Tube (flannery2010theinterleukin1receptorassociated pages 35-39, gosu2012molecularevolutionand pages 1-2, janssens2003functionaldiversityand pages 1-2).
2. Reaction Catalyzed  
   IRAK2 catalyzes the transfer of a phosphate group from ATP to specific serine/threonine residues on substrate proteins. In its kinase reaction, ATP reacts with a protein substrate containing serine/threonine residues to yield ADP and a phosphorylated protein, along with the release of a proton. This reaction typifies the canonical mechanism of protein kinases such as those in the IRAK family (hu2002regulationofil1 pages 5-6).
3. Cofactor Requirements  
   The catalytic activity of IRAK2, as with most serine/threonine kinases, requires divalent metal ion cofactors. In particular, Mg²⁺ is essential to coordinate the ATP molecule in the active site, thereby facilitating the transfer of the γ-phosphate group to target substrates (flannery2010theinterleukin1receptorassociated pages 5-9, li2002irak4anovel pages 1-2).
4. Substrate Specificity  
   IRAK2 phosphorylates substrate proteins that are components of intracellular signaling cascades, particularly those involved in Toll-like receptor (TLR) and interleukin-1 (IL-1) receptor pathways. Although comprehensive studies of IRAK2’s substrate consensus sequences are limited relative to more extensively characterized kinases, the general serine/threonine kinase mechanism implies that IRAK2 recognizes substrates with specific local motifs. Recent advances in the field of kinase substrate specificity—including the atlas of substrate specificities for the human serine/threonine kinome (Johnson2023Atlas) and intrinsic substrate specificity analyses for human tyrosine kinases (YaronBarir2024) – provide frameworks that could be applied to further elucidate IRAK2’s substrate selectivity. In the context of IRAK2 signaling, substrates include key adaptor and regulatory molecules such as TRAF6, components of the Myddosome complex, and downstream kinases in the MAPK cascade. However, the precise consensus motif for IRAK2 has not been fully established, and further studies are warranted to characterize its amino acid preferences (yeilding support from the priority publications in kinase specificity).
5. Structure  
   IRAK2 is organized into several distinct domains that contribute to both its catalytic and regulatory functions. At the N-terminus, IRAK2 contains a death domain that mediates interactions with adaptor proteins such as MyD88 and Mal/TIRAP. This death domain is critical for the assembly of the Myddosome complex upon receptor engagement (flannery2010theinterleukin1receptorassociated pages 43-47, janssens2003functionaldiversityand pages 6-7). Following the death domain, a proline/serine/threonine-rich (ProST) region is present; this region often contributes to protein–protein interactions and may also influence the stability of the protein. The central portion of IRAK2 harbors a kinase domain, which is structurally similar to other serine/threonine kinases and contains conserved motifs typical of enzymatic activity, such as an invariant ATP-binding lysine residue. This kinase domain is responsible for its catalytic function, even though certain studies have described IRAK2 as having atypical or regulatory catalytic activity rather than robust enzymatic phosphorylation measured in vitro (benosman2013interleukin1receptorassociatedkinase2 pages 1-3, meylan2008irak2takesits pages 1-2). At the C-terminus, IRAK2 contains one or more TRAF6-binding motifs that facilitate the assembly of signaling complexes and subsequent ubiquitination events necessary for downstream NF-κB activation (flannery2010theinterleukin1receptorassociated pages 43-47, keating2007irak2participatesin pages 5-6). Recent structural insights, including those derived from crystallographic studies of related IRAK kinases and predictive models provided by AlphaFold, support this overall domain organization and highlight key features such as the activation loop, a hydrophobic regulatory spine, and a C-helix that are common in kinases (gosu2012molecularevolutionand pages 14-15).
6. Regulation  
   IRAK2 is subject to multiple layers of regulation that control its activity and intracellular localization. Post-translational modifications play a central role in this regulation. For instance, upon receptor engagement (by IL-1 or TLR ligands), IRAK2 is phosphorylated – a process that is initiated by upstream kinases such as IRAK4, and may also involve autophosphorylation mechanisms (benosman2013interleukin1receptorassociatedkinase2 pages 1-3, meylan2008irak2takesits pages 2-2). In addition to phosphorylation, IRAK2 undergoes ubiquitination events that are crucial for the assembly and stabilization of the Myddosome. Notably, the interaction between IRAK2 and the E3 ubiquitin ligase TRAF6 leads to Lys63-linked polyubiquitination, an event that is critical for the propagation of NF-κB signaling (keating2007irak2participatesin pages 7-8, pauls2013twophasesof pages 7-8). Furthermore, recent studies have identified sumoylation as an additional regulatory modification; for example, IRAK2 is modified by RanBP2-mediated sumoylation, which is required for its translocation to the nucleus in response to LPS stimulation (zhou2017irak2directsstimulusdependent pages 16-19). These post-translational modifications influence IRAK2’s conformation, interactions with binding partners, and ultimately the duration and intensity of downstream signaling cascades.
7. Function  
   IRAK2 plays pivotal roles in mediating intracellular signaling downstream of the IL-1 type I receptor and multiple Toll-like receptors. Following engagement by IL-1, the receptor complex recruits IRAK2 via its death domain, which in turn participates in the formation of the Myddosome by assembling with MyD88, IRAK4, and IRAK1. This assembly is essential for the activation of downstream signaling pathways that lead to nuclear factor-κB (NF-κB) activation and subsequent transcriptional up-regulation of proinflammatory cytokine genes. In addition to regulating transcription, IRAK2 has been implicated in the stabilization of mRNA transcripts for cytokines and other inflammatory mediators—a function that is particularly evident in studies demonstrating its role in post-transcriptional control during endoplasmic reticulum stress as well as lipopolysaccharide-mediated immune responses (benosman2013interleukin1receptorassociatedkinase2 pages 1-3, hu2002regulationofil1 pages 5-6). IRAK2 is ubiquitously expressed in various tissues and immune cell types, where it functions as a critical mediator of innate immune responses. Its interactions with TRAF6 and involvement in the activation of downstream kinases such as TAK1 and members of the MAPK family (including JNK, p38, and ERK) position IRAK2 as a key regulator not only of inflammatory cytokine production but also of mRNA stability and processing events that control the amplification of immune signals (pauls2013twophasesof pages 1-2, yin2011thekinaseactivity pages 1-2).
8. Other Comments  
   Genetic variants and mutations in IRAK2 have been linked to altered immune responses and disease outcomes. For instance, specific non-synonymous single nucleotide polymorphisms (SNPs) such as the D431E variant have been associated with enhanced NF-κB activation through increased TRAF6 ubiquitination, thereby leading to elevated levels of proinflammatory cytokines (zhang2014interleukin1receptorassociatedkinase2 pages 1-2, zhang2014interleukin1receptorassociatedkinase2 pages 13-13). In addition, IRAK2 deficiency, such as that resulting from exon deletions, has been implicated in immune dysregulation disorders characterized by elevated inflammatory cytokine profiles and defective Myddosome assembly (fei2024irak2deficiencycauses pages 25-31). Despite its critical signaling functions, specific small molecule inhibitors that target IRAK2 remain to be fully developed and characterized, although IRAK family inhibitors more broadly have been explored for their therapeutic potential in inflammatory and neoplastic diseases (rhyasen2015iraksignallingin pages 5-6). Overall, IRAK2 is considered a promising therapeutic target given its central role in innate immune signal transduction, and ongoing research continues to elucidate its contributions to inflammatory pathologies and potential applications in drug development.
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