1. Phylogeny  
   IRAK2 is a member of the interleukin‐1 receptor‐associated kinase (IRAK) family, which comprises four proteins (IRAK1, IRAK2, IRAK3 [also known as IRAK‐M], and IRAK4) that are conserved throughout metazoans. IRAK2 has been identified in mammals with a single isoform in humans, although multiple splice variants exist in mice. The protein is evolutionarily related to other serine/threonine kinases within the Toll-like receptor (TLR) and interleukin‐1 receptor (IL‑1R) signaling pathways. Its orthologs are traceable across vertebrates, and phylogenetic analyses suggest that members of the IRAK family share a common ancestry with the Drosophila Pelle kinase, indicating a deep evolutionary conservation of innate immune signaling components (su2020irakfamilyin pages 1-5, janssens2003functionaldiversityand pages 2-3).
2. Reaction Catalyzed  
   The reaction catalyzed by IRAK2, as expected for a serine/threonine kinase, involves the transfer of the γ‑phosphate group from adenosine triphosphate (ATP) to specific serine or threonine residues on a substrate protein. In chemical terms, the reaction can be represented as:  
   ATP + [protein]‑(L‑serine or L‑threonine) → ADP + [protein]‑(L‑serine/threonine)‑phosphate + H⁺.  
   Although detailed substrate mapping for IRAK2 is not as extensively defined as for some other kinases, this generic phosphorylation reaction is congruent with its role in signal propagation following IL‑1 receptor engagement (cohen2009targetingproteinkinases pages 8-8).
3. Cofactor Requirements  
   Like most protein kinases, the catalytic activity of IRAK2 depends on the presence of divalent metal ions, with magnesium (Mg²⁺) being essential. Mg²⁺ ions coordinate ATP in the kinase active site to facilitate the transfer of phosphate groups to serine/threonine residues on target proteins. This cofactor requirement is in line with its classification as a serine/threonine kinase and is supported by the conservation of crucial ATP-binding residues in its catalytic domain (meylan2008irak2takesits pages 2-2).
4. Substrate Specificity  
   The substrate specificity of IRAK2 remains less completely characterized than that of several other kinases, yet experimental data suggest that, by virtue of its conserved kinase domain, IRAK2 preferentially phosphorylates serine/threonine residues within substrates involved in innate immune signaling. In particular, key functional studies indicate its role in phosphorylating or facilitating the activation of downstream components such as TRAF6 via a ubiquitination cascade. While a clear consensus phosphorylation motif is not definitively established for IRAK2 from the current literature, domains and critical lysine residues (e.g., Lys237) are implicated in its catalytic mechanism, suggesting that substrate motifs may involve basic residues in conjunction with flanking serine/threonine sites analogous to other IRAK family kinases (wang2013functionalandepidemiological pages 44-49, wang2013functionalandepidemiological pages 49-53).
5. Structure  
   IRAK2 exhibits a modular structure that is common to the IRAK family. Its domain organization is as follows:

• An N‑terminal death domain (DD) that mediates homotypic protein–protein interactions; this domain is critical for binding to the adaptor protein MyD88 and assembling into the myddosome complex. (flannery2010theinterleukin1receptorassociated pages 1-5, su2020irakfamilyin pages 1-5)

• A central ProST (proline-, serine-, threonine‑rich) domain which likely serves as a flexible linker region subject to extensive post‑translational modifications such as phosphorylation and ubiquitination. This region contributes to the scaffolding function during signal transduction (flannery2010theinterleukin1receptorassociated pages 5-9).

• A kinase domain that harbors the conserved motifs typical of serine/threonine kinases, including the invariant lysine residue (e.g., Lys237) essential for ATP binding. Although some studies have originally suggested that IRAK2 might be catalytically inactive due to substitutions at critical positions (for example, an asparagine replacing the aspartate in the catalytic loop), subsequent work indicates that IRAK2 is enzymatically active; structural studies have underscored the presence of an ATP‑binding pocket and a tyrosine gatekeeper residue that is characteristic of IRAK family members (cohen2009targetingproteinkinases pages 8-8, flannery2010theinterleukin1receptorassociated pages 5-9, wang2013functionalandepidemiological pages 44-49).

• A C‑terminal region that contains two TRAF6 binding motifs, which are necessary for propagating downstream signaling events through polyubiquitination processes. This region facilitates the recruitment and activation of TRAF6 and is instrumental in triggering NF‑κB activation (barbera2012activationmechanismsof pages 36-39, flannery2010theinterleukin1receptorassociated pages 5-9).

This overall structural organization supports IRAK2’s dual role as a kinase and as a scaffolding protein within protein complexes, and the presence of conserved structural features such as the catalytic loop, activation segment, and key residues in the kinase domain indicate its capacity for both catalytic phosphorylation and regulatory interactions (wang2013functionalandepidemiological pages 95-99, meylan2008irak2takesits pages 2-2).

1. Regulation  
   IRAK2 is subject to multiple layers of post‑translational regulation which modulate both its stability and activity. Key regulatory mechanisms include:

• Phosphorylation: IRAK2 undergoes autophosphorylation and is likely phosphorylated by interacting kinases such as IRAK4 within the myddosome complex. This phosphorylation is essential for its activation and for promoting a sustained NF‑κB signal following receptor stimulation. Specific phosphorylation events are implicated in modulating its interaction with downstream effectors and in controlling its catalytic activity (cohen2009targetingproteinkinases pages 8-8, flannery2011humaninterleukin1receptorassociated pages 1-2, wang2013functionalandepidemiological pages 95-99).

• Ubiquitination: IRAK2 interacts with TRAF6, and it plays a role in supporting TRAF6 polyubiquitination. This post‑translational modification is an essential step in activating downstream signaling pathways such as NF‑κB and MAP kinases. Although specific ubiquitination sites on IRAK2 are not fully mapped, the presence of TRAF6 binding motifs in its C‑terminal region underscores its function in facilitating ubiquitin‐chain formation as part of its regulatory role (zhang2014interleukin1receptorassociatedkinase2 pages 13-13, bahia2015interleukin1receptorassociated pages 3-4).

• Complex assembly: IRAK2 is recruited to the IL‑1R following ligand engagement and forms a multiprotein signaling complex known as the myddosome. This complex includes other IRAK family members (such as IRAK1 and IRAK4) and the adaptor MyD88. The assembly and subsequent disassembly of this complex are tightly regulated, ensuring that downstream signals are both initiated and eventually terminated appropriately. (flannery2010theinterleukin1receptorassociated pages 43-47, pereira2023regulationofinnate pages 1-2).

• Interactions with additional regulatory proteins: IRAK2 activity may be modulated by interacting proteins that either stabilize the protein complex or target proteins for degradation. In contrast to IRAK1, which contains PEST sequences that promote rapid degradation, IRAK2 lacks these sequences, thereby contributing to the sustained signaling observed during prolonged receptor stimulation (wang2013functionalandepidemiological pages 44-49, gan2006regulationsandroles pages 7-8).

These regulatory layers ensure that IRAK2 functions both as a signal amplifier and as a modulatory scaffold within TLR and IL‑1 receptor signaling pathways (flannery2010theinterleukin1receptorassociated pages 5-9, hu2002regulationofil1 pages 1-2).

1. Function  
   IRAK2 is functionally essential in mediating the cellular response initiated by interleukin‑1 type I receptor engagement. Its primary functions are summarized as follows:

• Signal propagation: Upon binding of IL‑1 to its receptor, the receptor complex recruits MyD88 which in turn engages IRAK family members. IRAK2 is then recruited to form the myddosome alongside IRAK4 and IRAK1. This assembly leads to the activation of downstream signaling cascades, particularly the NF‑κB and MAP kinase pathways. These cascades result in the transcriptional up‑regulation of pro‑inflammatory genes (flannery2010theinterleukin1receptorassociated pages 43-47, su2020irakfamilyin pages 1-5).

• mRNA stabilization: Beyond initiating transcription, IRAK2 plays a role in the post‑transcriptional regulation of cytokine mRNA by contributing to mechanisms that stabilize these mRNAs once they have been synthesized. This dual role in transcriptional and post‑transcriptional control enhances the amplitude and duration of the inflammatory response (Information section, cohen2009targetingproteinkinases pages 8-8).

• Sustained inflammatory signaling: IRAK2 is particularly important for sustaining NF‑κB activation during prolonged signaling. While IRAK1 may drive early-phase responses, IRAK2 appears critical for maintaining signaling during later phases of TLR stimulation, thereby ensuring a prolonged inflammatory response. This temporal regulation contributes to its role in chronic inflammatory conditions and autoimmune pathologies (flannery2010theinterleukin1receptorassociated pages 43-47, wang2013functionalandepidemiological pages 95-99).

• Interaction with downstream effectors: By binding to TRAF6 via its C‑terminal TRAF6 binding motifs, IRAK2 facilitates the formation of polyubiquitin chains that are essential for the activation of downstream effectors such as the TAK1 kinase complex. This molecular cascade culminates in the nuclear translocation of NF‑κB and activation of target gene transcription (barbera2012activationmechanismsof pages 36-39, flannery2010theinterleukin1receptorassociated pages 5-9).

Collectively, these functions underscore the pivotal role of IRAK2 in orchestrating the innate immune response by coupling receptor engagement to both transcriptional and post‑transcriptional regulatory mechanisms (flannery2011humaninterleukin1receptorassociated pages 1-2, pereira2023regulationofinnate pages 8-9).

1. Other Comments  
   IRAK2 is under active investigation due to its significant role in inflammation and innate immunity. Although specific small molecule inhibitors directly targeting IRAK2 are not well established, the kinase represents a promising target for the development of anti‑inflammatory and immunomodulatory therapeutic agents. Genetic studies and non‑synonymous single nucleotide polymorphisms (SNPs) in IRAK2 have been correlated with altered NF‑κB activity and variations in cytokine responses, which may affect disease outcomes in conditions such as sepsis, autoimmune diseases, and cancer (zhang2014interleukin1receptorassociatedkinase2 pages 13-13, wang2014acodingirak2 pages 2-3). In contrast to IRAK1, which has been the focus of several inhibitor studies, IRAK2’s unique contribution to sustained inflammatory signaling makes it a subject of considerable interest, particularly because its resistance to rapid degradation (owing to the lack of PEST sequences) allows for prolonged signal transduction (gan2006regulationsandroles pages 7-8, flannery2010theinterleukin1receptorassociated pages 5-9). Additionally, functional studies employing genetic knockout and RNA interference strategies have highlighted that loss of IRAK2 function may alter pro‑inflammatory cytokine production, further supporting its candidacy as a target in inflammatory disease therapies (wang2013functionalandepidemiological pages 95-99, ringwood2008theinvolvementof pages 1-2). The interplay between IRAK2 and its interacting partners, including MyD88, IRAK4, and TRAF6, continues to be an essential area of research in order to elucidate the precise molecular mechanisms governing its activity (flannery2010theinterleukin1receptorassociated pages 43-47, pereira2023regulationofinnate pages 1-2).
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